UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: **12/21/2017**

SUBJECT: **Pymetrozine**. Draft Human Health Risk Assessment for Registration Review

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Decision No.: 528651
Petition No.: NA
Risk Assessment Type: Single Chemical Aggregate
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40 CFR: §180.556

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The Pesticide Reevaluation Division (PRD) requested that the Health Effects Division (HED) conduct a draft risk assessment (DRA) for the insecticide, pymetrozine. This document contains HED's DRA to support registration review. It incorporates most recent data and assumptions for conducting dietary, residential, occupational, and aggregate exposure assessments.

Since the most recent human health risk assessment (D371299, Pymetrozine. Updated Aggregate Human Health Risk Assessment, 4/2/2010) and registration review scoping document (2013), HED has made the following changes to the pymetrozine risk assessment:

1) Updated the dietary exposure and risk assessment based on the most recent food consumption survey data, updated usage information, updated default processing factors and updated estimates of residues in drinking water;
2) Updated the residential exposure assessment using the 2012 Residential Standard Operating Procedures (SOPs) and body weights, as well as considered potential exposure from spray drift; and
3) Updated the occupational exposure assessment using the most recent unit exposure data and body weights.

1.0 Executive Summary

Pymetrozine is a selective insecticide and a member of the chemical class known as pyridine azomethines. It is currently registered for the control of a variety of sucking insect pests such as aphids and whiteflies on a number of agricultural field and orchard/vineyard crops. Tolerances are established for residues of pymetrozine in agricultural commodities in 40CFR §180.556. In addition, pymetrozine is registered for use on Christmas trees and ornamentals, including landscape ornamentals, ornamental plants in greenhouses, and interior plantscapes (interiorscapes). It is formulated as a water dispersible granule (WDG) end-use product. As a result of the registered uses, there is potential for exposure to pymetrozine residues through food and drinking water, from spray drift and contact with treated ornamentals in residential settings, and through occupational-related activities, such as mixing, loading, and applying.

Hazard Characterization

The toxicology database for pymetrozine is adequate for assessment of human health risk in accordance with the Food Quality Protection Act (FQPA). Immunotoxicity and subchronic inhalation toxicity studies are not available, but HED determined these studies were not needed. In mammals, the liver is the target organ for pymetrozine. In addition, there was evidence of neurotoxicity in the acute (ACN), subchronic (SCN), and developmental neurotoxicity (DNT) studies in rats. The neurological effects observed in the DNT have been used to assess risk associated with exposure to pymetrozine.

Increased prenatal susceptibility to pymetrozine was observed in the developmental toxicity studies in rats and rabbits as well as in the developmental neurotoxicity study (DNT), but not in the rat reproduction toxicity study. However, HED's degree of concern for the observed susceptibility is low because the selected endpoints are protective of the observed developmental effects and susceptibility. After evaluating the toxicological and exposure data, the pymetrozine risk assessment team has retained the required 10X FQPA Safety Factor (SF). In the DNT study a no-observed-adverse-effects-level (NOAEL) was not established for the brain effects (morphometric changes in pup brains) at the lowest-observed-adverse-effects-level (LOAEL) selected as the endpoint for risk assessment. Therefore, the 10X FQPA SF was retained in the form of a LOAEL-to-NOAEL extrapolation factor.

HED classified pymetrozine as a "likely human carcinogen" and recommended that quantification of risk be estimated for combined liver tumors (benign hepatomas and/or carcinomas) in male and female mice and female rats. The most potent unit risk, or slope factor (also referred to as the cancer potency factor), has been used for quantiation of cancer risk, and is based on male mouse liver benign hepatoma and/or carcinoma combined tumor rates. The pymetrozine cancer potency factor is 0.0119 $(mg/kg/day)^{-1}$ in human equivalents (TXR # 0014036, 3/9/2000). Pymetrozine has low acute toxicity, being classified as III or IV in the acute oral, dermal, inhalation, and eye/dermal irritation studies. Pymetrozine is regarded as a slight dermal sensitizer.

The morphometric changes observed in the brains of female pups on postnatal day (PND) 21, and on PND 63 in male pups in the DNT study in rats served as the basis for endpoint selection

for dietary (acute and chronic) residential (dermal and incidental oral) and occupational (dermal and inhalation) exposure and risk assessment. Although the morphometric changes were observed in pups, the effects could be attributed to *in utero* or post-natal exposure, and could be the result of a single or repeated doses. Therefore, the endpoint is considered relevant for acute (single dose), and short-term durations of exposure. However, since the dose selected for risk assessment was the lowest in the database, it was also used for chronic dietary risk assessment. Further, because of the susceptibility observed in the developmental and DNT studies, the oral endpoint and dose were also used for dermal and inhalation exposure and risk assessment,

The level of concern (LOC) for all dietary and non-dietary (residential) scenarios is 1,000, based on a 10X uncertainty factor (UF) for interspecies extrapolation, 10X for intraspecies extrapolation, and the FQPA SF of 10X retained as a LOAEL-to-NOAEL uncertainty factor (UF). For dietary assessments, these combined uncertainty factors were incorporated population adjusted doses (PADs). For occupational scenarios, the LOC of 1,000 is based on factors of 10X for interspecies extrapolation, 10X for intraspecies extrapolation, and a 10X LOAEL-to-NOAEL UF.

Dietary Exposure and Risk Assessment

Adequate residue chemistry data are available for the purpose of evaluating the registered uses of pymetrozine that could potentially result in dietary exposure. The residue chemistry database consists of adequate plant metabolism, animal metabolism, field trial, storage stability, rotational crop, and analytical method studies. There are no outstanding residue chemistry studies. The available monitoring data indicate that residues in most crops are generally non-detectable. In cases where detectable residues were found, they were considerably below the tolerance. For tolerance enforcement, the parent pymetrozine is the residue of concern. However, for risk assessment purposes, a number of metabolites/degradates are included for both crops (plants) and in drinking water. Degradates included in the drinking water estimates could not be excluded because they were structurally similar to the parent compound, or their potential toxicity could not be discounted.

HED conducted acute and chronic aggregate dietary (food and drinking water) exposure assessments using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA).

In the acute, chronic, and cancer dietary exposure assessments, residues in drinking water were the primary contributor to dietary exposure and risk. In the acute assessment, the most highly exposed population subgroup, All Infants, used 850% of the aPAD when residues in drinking water were included, regardless of whether or not residues in food were included. This same population subgroup used 19% of the aPAD when residues in food only were included. In the chronic assessment, the most highly exposed population subgroup, All Infants, used 240% of the cPAD when residues in drinking water were included, regardless of whether or not residues in food were included. This same population subgroup used <1% of the cPAD when residues in food only were included. In the cancer assessment, the risk estimate is 7.1×10^{-7} when residues

in food only are included. When residues in drinking water are included, as the EDWCs increase from 20 ppb to 367 ppb, the risk estimates increase from 5.0 x 10^{-6} to 9.1 x 10^{-5}.

Residential Exposure and Risk Assessment

Residential handler exposures are not expected because there are no registered or proposed residential uses that would result in handler exposure at this time. All registered pymetrozine product labels with residential use sites (e.g., garden and trees) require that handlers wear specific clothing (e.g., long sleeve shirt/long pants) and personal protective equipment (PPE) (e.g., gloves). Therefore, HED has made the assumption that these products are not for homeowner use, and has not conducted a quantitative residential handler assessment. However, residential post-application exposures are expected, and do not result in non-cancer risks of concern. Cancer risks for adults were also determined for pymetrozine residential post-application exposure, and range from 1.95×10^{-8} to 9.2×10^{-7}.

Spray Drift Exposure and Risk Assessment

Indirect exposure from drift from pesticide sprays applied to agricultural fields was considered for 50-foot-wide lawns where the nearest side of the property was directly adjoining the treated field. Adult dermal and children's (1 to <2 years old) combined dermal and incidental oral risk estimates from indirect exposure to pymetrozine are not of concern for lawns adjacent to the edge of the field.

Aggregate Exposure and Risk Assessment

Acute aggregate risk from exposure to pymetrozine results from exposure to residues in food and drinking water alone. The acute dietary exposure analysis included both food and drinking water; therefore, acute aggregate risk estimates are equivalent to the acute dietary risk estimates. Acute aggregate risk is of concern for the general U.S. population and all population subgroups.

Short-term aggregate risk assessments are needed for adults and children (6 to < 11 years), and include exposure through the dietary and dermal routes. In accordance with the FQPA, the dermal exposure is added to the background (food + water) chronic dietary exposure. For both adults and children 6 to less than 11, dermal exposure results from post-application contact with residues in treated gardens. For the short-term aggregate exposure assessment, this dermal exposure was added to background chronic dietary exposure. The combined MOEs were calculated and compared to the LOC of 1,000. For the cancer aggregate assessment, dermal exposure also results from post-application contact with residues in treated gardens. The dermal exposure was added to the background dietary exposure for the adult population subgroup with the highest exposure, Adults 20-49.

The short-term aggregate risk estimate is not of concern for children 6-<11 years of age, with an MOE of 1,000, which is equal to the LOC. However, the aggregate risk estimate is an MOE of 803 for adults, which is below the LOC of 1,000. The cancer dietary risk estimate for Adults 20-49 exceeds 1 x 10^{-6}; when the residential exposure is combined with the background dietary exposure, the cancer risk estimate increases from 9.2 x 10^{-5} to 9.3 x 10^{-5}. For both cancer and

non-cancer aggregate exposure estimates, the most significant contribution to aggregate exposure is background dietary exposure, largely due to the contribution from drinking water.

Occupational Exposure and Risk Assessment

Assuming label-specified clothing and PPE (i.e., baseline attire and gloves), two scenarios have risk estimates of concern (LOC = 1000):

1) mixing/loading WDG formulated products for aerial application on field crops (high/typical acreage, MOEs = 280 and 950, respectively); and
2) mixing/loading WDG formulated products for chemigation on field crops (high/typical acreage, MOEs = 950).

For the remaining scenarios, no other occupational handler combined risk estimates of concern were identified, with MOEs ranging from 1,100 to 1,100,000.

The occupational handler cancer risk estimates for the registered uses of pymetrozine ranged from 9×10^{-10} to 4×10^{-6} for private growers (assuming 10 days of exposure/year) and from 3×10^{-9} to 1×10^{-5} for commercial applicators (assuming 30 days of exposure/year), wearing label-specified clothing and PPE (i.e., baseline attire and gloves).

There are no occupational post-application dermal risk estimates of concern for activities and crops/use sites assessed, with dermal MOEs ranging from 2,400 to 690,000 (LOC = 1,000). The REI of 12 hours listed on the registered agricultural labels, is considered protective of post-application exposure. The occupational post-application cancer risk estimates for the registered uses of pymetrozine ranged from 3×10^{-10} to 5×10^{-7} for all activities and crops/use sites.

Environmental Justice

Potential areas of environmental justice concerns were considered in this human health risk assessment to the extent possible. Section 3.5: Considerations of Environmental Justice, discusses this topic in more detail.

Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include PHED 1.1, the AHETF database, the ORETF database, the ARTF database are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure.

2.0 HED Conclusions

2.1 Data Deficiencies

None

2.2 Tolerance Considerations

Tolerances for pymetrozine are listed in 40CFR §180.556. The residue of concern for tolerance enforcement is parent pymetrozine. The tolerance expression needs to be updated to address both coverage and compliance as delineated in HED's *Interim Guidance on Tolerance Expressions* (S. Knizner; 5/27/2009).

The tolerance expression in 40CFR §180.556 should be revised to state: "Tolerances are established for residues of pymetrozine, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only pymetrozine, 1,2,4-triazin-3(2H)-one,4,5-dihydro-6-methyl-4-[(3-pyridinylmethylene)amino], in or on the commodity."

Pymetrozine is registered on commodities that are part of crop groups or subgroups. The Agency has updated some of these groups and subgroups in the crop group regulation. The commodity definitions for pymetrozine have not been updated, however. HED recommends that these crop groups and subgroups be updated. The Vegetable, fruiting, group 8 tolerance of 0.2 ppm should be canceled and replaced with a tolerance at the same level for Vegetable, fruiting, group 8-10. Because of changes in the representative commodities for the leafy vegetable groups and subgroups and the establishment of the new group, Stalk, Stem, and Leaf Petiole Vegetable Group (22), the leafy vegetable group (Vegetable Leafy, Except Brassica, Group 4), the Brassica, Head and Stem, Subgroup 5A, and the Brassica, Leafy Greens Subgroup 5B, cannot be directly updated to the new and updated groups and subgroups. Instead, they should be replaced with the following groups and subgroups.

A tolerance of 0.04 ppm should be established for the Leafy greens subgroup, 4-16A. A tolerance of 0.25 ppm should be established for the Brassica leafy greens subgroup 4-16B. A tolerance of 0.5 ppm should be established for the Brassica head and stem group, 5-16. Tolerances should also be established for both subgroups of the crop group 22. A tolerance of 0.04 ppm shoud be established for Vegetable, stalk and stem, subgroup 22A, and a tolerance of 0.6 ppm should be established for Stalk, stem, and leaf petiole vegetable, subgroup 22B. Finally, tolerances should be established for three individual commodities that are now in crop subgroup 22A. HED is recommending in favor of a tolerance of 0.04 ppm for 22A; however, the tolerance for 22A is not adequate for these commodities. As a result, HED is recommending in favor of a tolerance of 0.6 ppm for celtuce and Florence fennel, and a tolerance of 0.5 ppm for kohlrabi. HED's tolerance recommendations are summarized in Tables 2.2.2.1 and 2.2.2.2, below.

2.2.1 Enforcement Analytical Method

An adequate HPLC/UV method is available for enforcement of the established tolerances. This method is AG-643A. Residues are extracted with 0.05 sodium borate:methyl alcohol, filtered,

concentrated, and cleaned up by column elution with ethyl acetate. The residues are then concentrated, reconstituted in acetone, and cleaned up on a silica solid-phase extraction cartridge eluted with methanol. The residues are evaporated to dryness, redissolved in the HPLC mobile phase, and analyzed by UV detection at 300 nm. The validated LOQ for pymetrozine is 0.02 ppm.

2.2.2 International Harmonization

Codex has not established pymetrozine MRLs for any commodity. As a result, harmonization with Codex is not an issue. Canada has established MRLs for most of the same commodities that have U.S. tolerances. The tolerances and MRLs are all harmonized. Mexico adopts either U.S. tolerances or Codex MRLs for its export purposes. The U.S. tolerances and Mexican MRLs are all harmonized. Harmonization with Codex or Mexico is not an issue.

The tolerance recommendations discussed above are summarized in the tables below.

TABLE 2.2.2.1. Tolerance Summary for Pymetrozine (40CFR §180.556)
Tolerances to be Established

Commodity	Current Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Leafy greens, subgroup 4-16A	None	0.04	Updated crop group tolerance
Brassica, leafy greens, subgroup 4-16B	None	0.25	Updated crop group tolerance
Brassica, head and stem, Group 5-16	None	0.5	Updated crop group tolerance
Vegetable, stalk and stem, subgroup 22A	None	0.04	Updated crop group tolerance
Stalk, stem, and leaf petiole vegetable, subgroup 22B	None	0.6	Updated crop group tolerance
Celtuce	None	0.6	These commodities are now in Subgroup 22A. HED is recommending in favor of a tolerance of 0.04 ppm for 22A; however, the tolerance for 22A is not adequate for these commodities. As a result, HED is recommending in favor of individual tolerances.
Florence Fennel	None	0.6	
Kohlrabi	None	0.5	
Vegetable, fruiting, group 8-10	None	0.2	Updated crop group tolerance

TABLE 2.2.2.2. Tolerance Summary for Pymetrozine (40CFR §180.556)
Tolerances to be Canceled

Commodity	Current Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Asparagus	0.04	None	Cancel (Asparagus is in subgroup 22A
Vegetable, leafy, except Brassica, group 4	0.6	None	Cancel
Brassica, head and stem, subgroup 5A	0.5	None	Cancel
Brassica, leafy greens, subgroup 5B	0.25	None	Cancel

TABLE 2.2.2.2. Tolerance Summary for Pymetrozine (40CFR §180.556) Tolerances to be Canceled			
Commodity	**Current Tolerance (ppm)**	**Recommended Tolerance (ppm)**	**Comments; *Correct Commodity Definition***
Turnip greens	0.25	None	Cancel (Turnip greens are in 4-16B)
Vegetable, fruiting, group 8	0.2	None	Cancel

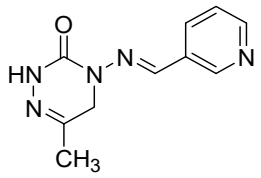
2.3 Label Recommendations

Various non-cancer risk estimates of concern were identified for occupational handlers; changes in the pymetrozine product labels could mitigate those risks. In addition, there are cancer risk estimates for occupational handlers that exceed 1×10^{-6}. Finally, HED notes that respirators are required on the labels as a condition of the HASPOC decision (TXR # 0056567, 3/20/2013) not to require the subchronic inhalation study.

3.0 Introduction

3.1 Chemical Identity

The chemical structure and nomenclature are given in the table below.

Table 3.1. Pymetrozine Nomenclature.	
Chemical Structure	
Empirical Formula	$C_{19}H_{24}O_3$
Common Name	Pymetrozine
Company Experimental Name	CGA-215944
IUPAC Name	(*E*)-4,5-dihydro-6-methyl-4-(3-pyridinylmethyleneamino)-1,2,4-triazin-3(2*H*)-one
CAS Name	(*E*)-4,5-dihydro-6-methyl-4-[(3-pyridinylmethylene)amino]-1,2,4-triazin-3(2*H*)-one
CAS Registry Number	123312-89-0
End-use Product/EP	Fulfill® (EPA Reg. No. 100-912; 50% ai WDG) Endeavor® (EPA Reg. No. 100-913; 50% ai WDG)
Chemical Class	Pyridine Azomethine

3.2 Physical/Chemical Characteristics

Pymetrozine has a water solubility of 290 ppm at 25°C, which indicates that it is relatively soluble in water. It has a low octanol/water partition coefficient, log K_{ow}, of -0.18, which

indicates that it is slightly more likely to partition into an aqueous phase than an organic phase. As a result, it does not bioaccumulate. It has a low vapor pressure of 3.0×10^{-8} mm Hg. As a result, it does not volatilize to a significant extent.

3.3 Pesticide Use Pattern

Pymetrozine is a selective insecticide and a member of the chemical class known as pyridine azomethines. It is registered for the control of a variety of sucking insect pests such as aphids and whiteflies on a number of agricultural field and orchard/vineyard crops. In addition, it is registered for use on Christmas trees and ornamentals, including landscape ornamentals, ornamental plants in greenhouses, and interior plantscapes (interiorscapes). It is formulated as a water dispersible granule (WDG) end-use product. All registered labels require baseline attire (i.e., long-sleeved shirt, long pants, shoes and socks) in addition to chemical resistant gloves. The restricted entry interval (REI) on all registered agricultural labels is 12 hours. Table F.1 contains an overview of the maximum application rates for each use site considered for the residential and occupational assessments. For more detailed crop-specific uses, see Appendix F.2. The maximum single application rates listed on the most current labels were used to estimate exposure and risk to pymetrozine.

3.4 Anticipated Exposure Pathways

Humans could be exposed to pymetrozine residues from consuming plant commodities containing residues resulting from agricultural applications. The agricultural applications can result in pymetrozine residues reaching surface and groundwater, both of which can serve as sources of drinking water. There is also potential for residential post-application exposure via the dermal route of exposure, as well as non-occupational bystander dermal and incidental oral (children only) exposure to spray drift from occupational applications. In addition, occupational workers can be exposed during mixing, loading, and applying the chemical, as well as during post-application activities in treated fields.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups, and exposure assessments are performed when conditions or circumstances warrant. Whenever

appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure, and it was considered in this analysis. Further considerations are also currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The toxicology database is considered adequate for assessment of human health risk from exposure to pymetrozine. The HED Hazard and Science Policy Council (HASPOC) determined that an immunotoxicity study was not needed because, based on lack of evidence of immunotoxicity in the current database, the study would not be expected to provide a more sensitive endpoint or result in a lower point of departure (POD) than currently selected for the overall risk assessment (TXR #0056921, 3/27/2014). Additionally, HASPOC determined that a subchronic inhalation toxicity study was not needed because the oral POD used for assessing inhalation risk was based on the most sensitive endpoint observed in the most sensitive population subgroup (i.e., an inhalation study would not yield a lower POD) (TXR# 0056567, 3/20/2013). A literature search was conducted for pymetrozine, but no applicable studies were found that would impact human health risk assessment. In the guideline toxicity studies, pymetrozine was evaluated for the following:

- Rat, mouse, and dog 90-day subchronic oral toxicity
- Rat 28-day dermal toxicity
- Rat and rabbit developmental toxicity
- Rat two-generation reproductive toxicity
- Rat, mouse, and dog chronic and/or carcinogenicity toxicity
- Rat neurotoxicity (acute, subchronic, and developmental [DNT])
- Rat single and repeated-dose metabolism
- Complete genotoxicity battery
- Rat dermal penetration study

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

The ADME of pymetrozine (0.5 and 100 mg/kg/day) was examined in single and repeated-dose studies in rats. Pymetrozine showed rapid absorption, distribution, and no significant sex differences following oral and intravenous (iv) administration with time to maximum blood concentrations (T_{max}) of 0.3 ppm and 60 ppm occurring at 15 minutes and 4 hours within the low and high doses, respectively. Pymetrozine was well absorbed in all dose groups (52-85% of the administered dose [AD]). Calculated half-life times ($t_{½}$) for the depletion of radiolabel from all the tissues ranged from 1 to 2 hours at the 0.5 mg/kg dose (pyridine and triazine labels) and from 2 to 11 hours at the 100 mg/kg dose, with the pyridine label having a relatively longer $t_{½}$ than the triazine label. The area under the curve (AUC) values were unaffected by labeling site but were

~800 fold higher at the high dose compared to the low dose. Tissue residue levels were the highest in the kidney and liver. Tissue residue levels peaked at 15 minutes in the low dose (both labels), and at 4 to 11 hours at the high dose, with the pyridine label taking a relatively longer time to peak than the triazine label. Additionally, greater than 90% of the administered dose of pymetrozine was eliminated within 7 days of exposure.

The largest portion of the AD was elimination in the urine; 52-73.5% after 24 hours and 56.3-80.3% after 7 days. Other significant sources of excretion (determined after 7 days) included expired air (0.2-0.7%), and feces (15.4-38.9%). Biliary excretion was higher for the low dose compared to the high dose, with up to 30% excretion in the low dose and 18% in the high dose indicating some saturation of absorption. After a high dose was administered, 12 urinary and fecal metabolites were recovered, isolated, and characterized. Unchanged pymetrozine (~20%) was detected as well. There was a relatively high level of unchanged test material in the urine at the high dose of 100 mg/kg, suggesting metabolic saturation. Three major metabolic pathways were observed: 1) oxidation of the methyl substituent at the triazine ring which was further oxidized to corresponding carboxylic acid; 2) oxidation at methylene group within the triazine ring; and 3) cleavage of the bridge between the two rings giving rise to several single ring metabolites. There was no indication that conjugated metabolites were formed.

4.2.1 Dermal Absorption

An *in vivo* dermal absorption study in the rat indicated dermal penetration was less than 1%, not including material that adhered to the skin (MRID 44024958). HED reviewed this study (TXR # 0013439, 6/18/1999) and concluded that the amount of the dose absorbed after skin washing increased slowly with time, suggesting limited absorption of the remaining radioactivity in the skin. Additionally, the amount remaining in or on the skin did not increase with increasing exposure duration. When the slow absorption rate is considered in conjunction with normal skin desquamation, it is very unlikely that pymetrozine associated with the entire skin would be bioavailable. HED also determined that the low amount of radioactivity used may have compromised the detectability of the actual penetration. Based on these considerations, it was determined that an upper bound 1% dermal absorption factor would be appropriate for risk assessment purposes. The lack of toxicity observed in the rat 28-day dermal toxicity study is consistent with low absorption via the dermal route.

4.3 Summary of Toxicological Effects

The liver is the target organ for pymetrozine. Subchronic exposures resulted in necrosis (mouse and dog) and bile duct proliferation (dog only). Increased liver weights and hypertrophy were also noted in several studies. Additional effects seen in rats via the oral route included leukocytosis, bilirubininuria (females), calcification of kidneys (males), and atrophy of the thymus; however, no effects were seen in a route-specific dermal toxicity study up to 1000 mg/kg/day. In dogs, skeletal muscle atrophy, lymphocytic infiltration, and anemia were also observed following subchronic exposure. Following chronic exposures, an increased incidence of liver tumors (benign hepatomas and/or carcinomas) was observed in rats and mice, and the CARC classified pymetrozine as a "likely human carcinogen" (see Section 4.5.3).

Increased quantitative susceptibility to pymetrozine was observed in the developmental toxicity studies in rats and rabbits as well as in the developmental neurotoxicity study (DNT), but not in the rat reproduction toxicity. In the rat developmental toxicity study, fetal skeletal anomalies (such as poor or absent ossification and dumbbell shaped thoracic vertebral centers) were observed at the highest dose tested (300 mg/kg/day), while no adverse effects were evident in maternal toxicity at the same dose. Similarly, in the rabbit developmental toxicity study, fetal skeletal anomalies were observed, including increased incidences of 13th ribs, fused sternebrae, and delayed ossification of digits, at 75 mg/kg/day, while no adverse effects were evident in maternal animals up to the highest dose tested (125 mg/kg/day). In the rat DNT, brain morphometric changes (considered to be adverse) occurred in the offspring at the lowest dose tested (8.1 mg/kg/day), while maternal toxicity consisting of complete litter losses was observed at higher doses (38.7 mg/kg/day). However, in the rat reproductive toxicity study, offspring and maternal toxicity occurred at the same dose level. There was decreased body weight in the pups during lactation, and some delay in eye opening. Parental toxicity included decreased body weight, body weight gain, and food consumption, as well as liver effects.

There was evidence of neurotoxicity in the rat acute, subchronic, and developmental neurotoxicity studies in rats. In the acute study, there was a transient decrease in the body temperature and decreased activity at the low dose (125 mg/kg/day) along with tremors, decreased mobility, and abnormal hindlimb positioning observed at higher doses. In the subchronic neurotoxicity study in rats, stereotypy in males and tiptoe gate (walking on toes) in females were observed at the high dose; however, the frequency and magnitude of these effects were low. In the DNT, morphometric changes in the brains of pups occurred at the lowest dose tested (8.1 mg/kg/day) without any effects on functional endpoints. However, there was a technical failure in the auditory startle response evaluations, so the functional measures might not have been adequately assessed. Therefore, for the purpose of risk assessment the brain morphometric changes in pups are assumed to be adverse with respect to fetal development, even in the absence of functional measures.

Pymetrozine has low acute toxicity, being classified as III or IV in the acute oral, dermal, inhalation, and eye/dermal irritation studies. Pymetrozine is regarded as a slight dermal sensitizer.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[1]

After evaluating the toxicological and exposure data, the pymetrozine risk assessment team recommends that the 10X FQPA SF be retained in the form of a LOAEL-to-NOAEL extrapolation factor based on the selection of the pup LOAEL for endpoint (brain morphometric changes) and dose selection, and for the observed quantitative susceptibility. EPA concludes that retention of the 10X factor will be protective of the observed susceptibility for the following reasons: 1) The toxicity database for pymetrozine is complete for purpose of conducting an FQPA assessment, including developmental toxicity studies in the rat and rabbit, a two-generation reproduction study in the rat, and acute, subchronic, and developmental neurotoxicity studies in the rat. 2) While there is concern for the quantitative susceptibility observed in pups in

[1] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

the DNT study, the brain morphometric changes were observed in the absence of impacts on developmental landmarks, clinical signs, FOB, motor activity, learning and memory, and brain weights. The dose response of the morphological changes and the minimal effects at the LOAEL suggest that 8.1 mg/kg/day is a threshold dose for the effect. The use of the DNT LOAEL for the point of departure for the aPAD is therefore considered to be conservative for the reasons discussed above. 3) There is concern for the quantitative susceptibility observed in pups in the rat and rabbit developmental toxicity studies; however, these effects do not result in a lower POD than the dose currently selected, which is protective of all effects in the database. 4) The only potential nondietary exposure for infants/young children is associated incidental oral exposure post-applicatoin exposure associated with potential drift from agricultural applications. 5) The acute, chronic, and cancer assessments are conservative assessments based on anticipated residues from crop field trials. These anticipated residues account for parent and all metabolites of concern. The acute assessment is based on 100% crop treated (PCT) assumptions, while the chronic assessment includes PCT estimates. For commodities for which usage data were not available, HED assumed 100% PCT. 6) The dietary assessment incorporated drinking water residue estimates generated by models and associated modeling parameters which are designed to provide conservative, high-end estimates of water concentrations. 7) The overall exposure assessment does not underestimate potential exposure and risk associated with agricultural uses of pymetrozine.

4.4.1 Completeness of the Toxicology Database

The toxicology database for pymetrozine is complete and adequate for an FQPA evaluation, including developmental toxicity studies in rats and rabbits; a two-generation reproduction toxicity study in rats; and acute, subchronic, and developmental neurotoxicity studies in rats.

Study deficiencies were identified in the DNT, but did not preclude use of the study endpoint selection and risk assessment: 1) there was technical failure of the recording equipment for auditory startle resulting in a lack of data for 3 rats/dose on postnatal day (PND) 23, one control on PND 61, and three rats in the 500 ppm group on PND 61. However, HED determined that the missing data did not significantly impact the study results; 2) The DNT was classified as acceptable/non-guideline because the positive control data have not been reviewed. Positive control data were submitted for tail flick response, learning and memory, motor activity, functional observational battery (FOB), and neuropathology. HED is currently in the process of reviewing the positive control data for the all the submitted DNT studies, including the pymetrozine DNT study. However, until all of the control data have been reviewed, the DNT will be classified as acceptable/non-guideline but adequate for regulatory purposes.

4.4.2 Evidence of Neurotoxicity

There is evidence of neurotoxicity in the ACN, SCN, and DNT in rats (see Section 4.3); however, the degree of concern for the observed neurotoxicity is low because: 1) there were no corroborating neuropathological findings; and 2) the selected endpoint and dose are protective of these effects.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There was evidence of quantitative pre-natal susceptibility in both the rat and rabbit developmental toxicity studies and in the DNT (see Section 4.3). [In the DNT it is not possible to determine whether or not the morphometric changes were the result of pre-natal or post-natal dosing.] However, the degree of concern concern for the susceptibility is low because the selected endpoints and doses are protective of the observed developmental effects and the observed susceptibility.

4.4.4 Residual Uncertainty in the Exposure Database

The residual uncertainties with respect to dietary or residential exposure are low. The dietary exposure assessments are based on the most conservative endpoint and reflect the most conservative assumptions with respect to the relevant lifestages; therefore the dietary assessment is protective of all other endpoints and populations of concern. Furthermore, conservative, upper-bound assumptions were used to determine exposure through drinking water, such that these exposures have not been underestimated. Therefore, the actual risk from exposure to pymetrozine will likely be much lower than HED's risk estimates conducted for the existing uses. In addition, the residential exposure estimates are based on the 2012 Residential SOPs, are conservative, and do not underestimate exposure and risk.

4.5 Toxicity Endpoint and Point of Departure Selections

Table 4.5.4.1 summarizes the toxicological doses and endpoints selected for dietary andnon-occupational risk assessments, and Table 4.5.4.2 summarizes the toxicological does and endpoints selected for occupational risk assessments. The rationale for the dose/endpoint selection is described below.

4.5.1 Dose-Response Assessment

It is recognized that some of the studies in the pymetrozine database have not been updated to reflect current practices in hazard evaluation, and the NOAELs and LOAELs might be considered conservative. The currently selected points of departure (PODs) are protective of the effects observed in the pymetrozine database, and any updates to these studies would not impact the overall findings of the risk assessment (i.e., would result in higher NOAEL/LOAEL values).

The developmental neurotoxicity (DNT) study in rats served as the basis for endpoint selection for residential (incidental oral, dermal, and inhalation) and occupational (dermal and inhalation) exposure and risk assessment. In the study, morphometric changes in the brains of female pups were observed on postnatal day (PND) 21, and on PND 63 in male pups. Since the morphometric changes could be due to either pre- or postnatal exposure, the endpoint is relevant for pregnant females (residential post-application and occupational handlers) and for offspring (children exposed post-application in residential settings). Therefore, the endpoint is relevant for oral, dermal, and inhalation assessments. For the incidental oral assessments, the route and duration of the DNT study are appropriate. For the dermal assessments, HED could not rely on the route-specific dermal toxicity study because it would not account for the increased susceptibility observed in the DNT study. Additionally, in the absence of a route-specific

inhalation study, the oral DNT study was used for inhalation risk assessment, and the DNT endpoint is protective of all other effects in the database.

In the DNT study, the morphometric brain changes occurred at the lowest-observed-adverse-effects level (LOAEL) of 8.1 mg/kg/day. A no-observed-adverse-effects-level (NOAEL) was not identified. Therefore, the level of concern (LOC) for all scenarios is 1000; for residential scenarios this includes 10X for interspecies extrapolation, 10X for intraspecies extrapolation, and the FQPA SF of 10X retained as a LOAEL-to-NOAEL uncertainty factor (UF). For occupational scenarios, the LOC of 1000 is based on factors of 10X for interspecies extrapolation, 10X for intraspecies extrapolation, and a 10X LOAEL-to-NOAEL UF.

4.5.2 Recommendations for Combining Routes of Exposures for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major sources (oral, dermal, and inhalation) and determine whether the individual exposures can be combined. Since the same study/effects were chosen for assessment of incidental oral, inhalation, and dermal exposures, exposures from these routes may be combined.

4.5.3 Cancer Classification and Risk Assessment Recommendation

In the combined chronic toxicity/carcinogenicity study in rats, the incidence of benign hepatoma in females at the mid and high dose was increased relative to controls and was outside the historical control range. This effect was not observed in males. Furthermore, in female and male mice, the incidence of liver carcinomas and combined hepatomas and/or carcinomas associated with the higher doses of pymetrozine was increased relative to the controls and was outside of the historical range. The dose levels selected were considered adequate to assess the carcinogenic potential of pymetrozine in rats and mice. The available genotoxicity studies did not indicate genotoxic potential. Limited mode-of-action data submitted for pymetrozine were considered insufficient to identify a non-linear mode of action or affect the classification of carcinogenicity.

In accordance with the EPA *Proposed Guidelines for Carcinogen Risk Assessment* (4/23/1996), the CARC classified pymetrozine as a "likely human carcinogen" and recommended that quantification of risk be estimated for combined liver tumors (benign hepatomas and/or carcinomas) in male and female mice and female rats. The most potent unit risk, or slope factor for pymetrozine has been used to quantify cancer risk; the pymetrozine cancer potency factor is based on male mouse liver benign hepatoma and/or carcinoma combined tumor rates, and is equivalent to 0.0119 $(mg/kg/day)^{-1}$ in human equivalents.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Health Risk Assessment

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Pymetrozine for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations)	Offspring LOAEL = 8.1 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF/ UF_L = 10X	Acute RfD = 0.081 mg/kg/day aPAD = 0.008 mg/kg/day	**Developmental Neurotoxicity (Rat)** Offspring LOAEL = 8.1 mg/kg/day, based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63.
Chronic Dietary (All Populations)	Offspring LOAEL = 8.1 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF/UF_L = 10X	Chronic RfD = 0.081 mg/kg/day cPAD = 0.008 mg/kg/day	**Developmental Neurotoxicity (Rat)** Offspring LOAEL = 8.1 mg/kg/day, based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63.
Incidental Oral Short-Term (1-30 days) and Intermediate-Term (1-6 months)	Offspring LOAEL = 8.1 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF/UF_L = 10X	Residential LOC for MOE = 1000	**Developmental Neurotoxicity (Rat)** Offspring LOAEL = 8.1 mg/kg/day, based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63.
Dermal Short- (1-30 days) and Intermediate-Term (1-6 months)	Offspring LOAEL = 8.1 mg/kg/day DAF = 1%	UF_A = 10X UF_H = 10X FQPA SF/UF_L = 10X	Residential LOC for MOE = 1000	**Developmental Neurotoxicity (Rat)** Offspring LOAEL = 8.1 mg/kg/day, based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63
Inhalation Short- (1-30 days) and Intermediate-Term (1-6 months)	Offspring LOAEL = 8.1 mg/kg/day Inhalation toxicity assumed to be equivalent to oral toxicity	UF_A = 10X UF_H = 10X FQPA SF/UF_L = 10X	Residential LOC for MOE = 1000	**Developmental Neurotoxicity (Rat)** Offspring LOAEL = 8.1 mg/kg/day, based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63
Cancer (oral, dermal, inhalation)	Classification: "likely human carcinogen." A cancer potency factor of 0.0119 $(mg/kg/day)^{-1}$ was calculated for pymetrozine based on male mouse liver combined benign hepatoma and/or hepatocarcinoma.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = extrapolation from LOAEL to NOAEL. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose (a = acute, c = chronic). DAF = Dermal Absorption Factor. MOE = margin of exposure. LOC = level of concern.

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Pymetrozine for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- (1-30 days) and Intermediate-Term (1-6 months)	Offspring LOAEL = 8.1 mg/kg/day DAF = 1%	UF_A = 10X UF_H = 10X UF_L = 10X	Occupational LOC for MOE = 1000	**Developmental Neurotoxicity (Rat)** Offspring LOAEL = 8.1 mg/kg/day, based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63
Inhalation Short- (1-30 days) and Intermediate-Term (1-6 months)	Offspring LOAEL = 8.1 mg/kg/day Inhalation toxicity assumed to be equivalent to oral toxicity	UF_A = 10X UF_H = 10X UF_L = 10X	Occupational LOC for MOE = 1000	**Developmental Neurotoxicity (Rat)** Offspring LOAEL = 8.1 mg/kg/day, based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63
Cancer (oral, dermal, inhalation)	Classification: "likely human carcinogen." A cancer potency factor of 0.0119 $(mg/kg/day)^{-1}$ was calculated for pymetrozine based on male mouse liver combined benign hepatoma and/or hepatocarcinoma.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = extrapolation from LOAEL to NOAEL. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose (a = acute, c = chronic). DAF = Dermal Absorption Factor. MOE = margin of exposure. LOC = level of concern.

4.6 Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for pymetrozine, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), pymetrozine is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA

will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[2] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[3]

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

The registrant submitted plant metabolism studies on tomatoes, potatoes, rice, tobacco, and cotton. The available data indicate that pymetrozine is initially oxidized at the 5-methylene group on the triazine ring to form Metabolite 2U (CGA-359009) and CGA-323584. CGA-323584 is then hydrolyzed at the enamino double-bond to form CGA-294849 and CGA-300407. The triazine-ring metabolite, CGA-294849, is then subsequently deaminated to form GS-23199, which undergoes conjugation with sugars. Pymetrozine can also be directly hydrolyzed at the enamino bridge to form CGA-249257 and CGA-180778, which is further oxidized to form CGA-180777. In tobacco and rotational crops, CGA-180777 was further methylated on the pyridine ring to form CGA-96956. Formation of pyrazolidinone was observed from cleavage of the parent in tobacco.

5.1.2 Summary of Environmental Degradation

Major routes of environmental dissipation of pymetrozine following application include spray drift and runoff on eroded sediment/soil as well as transformation. As a result, pymetrozine and pymetrozine transformation products may reach surface waters used as source drinking water. A major route of transformation is expected to be through aqueous photolysis in clear and shallow waterbodies (half-life = 3 days); however, in deep ponds, lakes, or reservoirs, anaerobic aquatic metabolism is expected to dominate the dissipation processes (half-life = 89 days). Pymetrozine transformation via aerobic aquatic metabolism ranges in half-lives of 15 to 527 days. Hydrolysis was only observed in acidic conditions (pH ≤ 5) with a half-life of 23 days. Pymetrozine is persistent in neutral and basic aqueous environments.

[2] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[3] http://www.epa.gov/endo/

Pymetrozine is stable to soil photolysis, though there are inconsistencies in the data. Microbial-mediated transformation is biphasic, described by a quick rate of decline, followed by a slower rate until study termination. Laboratory aerobic soil metabolism half-lives range from 4 to 238 days. In most studies, pymetrozine was mineralized to carbon dioxide by microbial activity, ranging from 22% to 73% of the applied radioactivity by study termination.

It is not as likely for parent pymetrozine to be found in groundwater used as source drinking water because it is not expected to leach very deep through the soil profile. However, in areas with karst soils or where macro particle transport through the soil occurs, or in cases of a shallow water table, pymetrozine could reach groundwater. Pymetrozine was observed to be slightly mobile under actual use conditions in field studies located in California, Georgia, and New York. These half-life values were biphasic and ranged from 39 to 269 days, and were consistent with laboratory metabolism studies. Two field lysimeter studies detected pymetrozine primarily within the surface soil horizons, but as deep as 30 inches, and also in the leachate.

Batch equilibrium studies indicate relatively high adsorption of pymetrozine to soil for all soils tested, and approximately 90% of pymetrozine adsorption occurred within the first two hours. Clay content had the strongest relationship to pymetrozine adsorption ($r^2 = 0.87$). Organic matter, cation exchange capacity, and pH also directly relate to pymetrozine adsorption. According to the FAO Mobility Classification Scale, and based on study-specific K_{oc} values (1,394 – 7,875 mL/g-OC; n=6) from batch equilibrium studies, pymetrozine is considered slightly mobile in soil (average K_{oc}= 3,936 mL/g-OC). Likewise, column leaching studies of parent and aged parent indicate that pymetrozine exhibits slight mobility to no mobility in sand, sandy loam, loam, and silty clay loam soil columns.

5.1.3 Comparison of Metabolic Pathways

Three major metabolic pathways were observed in rats: 1) oxidation of the methyl substituent at the triazine ring which was further oxidized to the corresponding carboxylic acid; 2) oxidation at the methylene group within the triazine ring; and 3) cleavage of the bridge between the two rings giving rise to several single ring metabolites. There was no indication that conjugated metabolites were formed. These same metabolic processes take place in plants, with the exception that in plants, the deaminated triazine ring metabolite undergoes conjugation with sugars. As the same metabolites formed in the rat and in plants, the toxicity of the plant metabolites is accounted for in the rat toxicity studies.

5.1.4 Residues of Concern Summary and Rationale

HED has determined that parent pymetrozine is the residue of concern in plants for tolerance enforcement. The residues of concern in plants for risk assessment are pymetrozine, GS-23199, CGA-294849, CGA-215525, and CGA-249257. The registrant submitted acceptable goat metabolism studies. Metabolite CGA-313124 and its phosphate conjugate should also be analyzed in feeding studies for inclusion in risk assessment and possibly in tolerances as well. Livestock commodity tolerances have not been established; therefore, it is not necessary to determine the residue of concern for risk assessment at this time. The registrant also submitted an acceptable poultry metabolism study. HED did not make a decision as to the residues of concern in poultry because tolerances are not needed at this time.

Table 5.1.4. Summary of Metabolites and Degradates to be included in the Pymetrozine Risk Assessment and Tolerance Expression			
Matrix		**Residues Included In Risk Assessment**	**Residues Included In Tolerance Expression**
Plants	Primary Crop	Pymetrozine, GS 23199, CGA 215525, CGA 249257, CGA 294849[1]	Pymetrozine
	Rotational Crop	Not Applicable	Not Applicable
Livestock	Ruminant	Not Applicable	Not Applicable
	Poultry	Not Applicable	Not Applicable
Drinking Water		Pymetrozine, CGA 359009, CGA 366431, CGA 363430, CGA 294849, CGA 215525, Hydroxy CGA 215525	Not Applicable

[1] GS 23199 can serve as a marker compound for CGA 215525, CGA 249257, and CGA 294849

5.2 Food Residue Profile

Adequate residue data are available for the purpose of evaluating the registered uses of the pymetrozine that could potentially result in dietary exposure. The residue chemistry database consists of adequate plant metabolism, animal metabolism, field trial, storage stability, rotational crop, and analytical method studies. There are no outstanding residue chemistry studies.

HED examined the Pesticide Data Program monitoring data taken between 2010 and 2015. In most samples, residues were non-detectable. In cases where PDP did find detectable residues, the residues were considerably below the tolerance. Of the commodities PDP analyzed, tomatoes and cherry tomatoes had detectable residues most often.

5.3 Water Residue Profile

EFED prepared a drinking water assessment (DWA) for pymetrozine (J. Joyce and R. Bohaty, D439606, 8/24/2017). The following information relevant to the pymetrozine dietary exposure assessments is excerpted from that memorandum: "The DWA was completed using current models and guidance. Parent pymetrozine and six transformation products (CGA 359009, CGA 363431, CGA 363430, CGA 215525, Hydroxy CGA 215525, and CGA 294849) are the residues of concern considered per the Residues of Concern Knowledgebase Subcommittee (ROCKS) memorandum. All residues are assumed to have similar toxicity to parent, therefore, a total toxic residue (TTR) approach was utilized. Parent-only pymetrozine results are provided for comparison.

All modeled use scenarios were developed based on pymetrozine registered labels and in consultation with the Biological and Economic Analysis Division (BEAD) of the Office of Pesticide Programs (OPP). Estimated drinking water concentrations (EDWCs) for surface water and groundwater for pymetrozine and total toxic pymetrozine residues are provided in Table 5.3.1. In addition to providing EDWCs for maximum label use rates, EDWCs for use on potatoes (a major use for pymetrozine) based on typical application rates are also included for characterization.

Based on maximum label use rates, TTR EDWCs from sourced surface water are not expected to exceed 47 µg/L as the daily average surface water concentration, 13 µg/L for the 1 in 10 year-annual average, and 10 µg/L for the 30-year annual average in the dietary risk assessment. EDWCs resulting from groundwater from vulnerable wells are not expected to exceed 404 µg/L as the peak groundwater concentration, and 367 µg/L as the post-breakthrough average. The EDWCs decrease by approximately 5X when typical use rates are utilized, and are not expected to exceed 89 µg/L as the peak groundwater concentration, and 79 µg/L as the post-breakthrough average.

EFED recommends that the Health Effects Division (HED) use 404 µg/L as the peak groundwater concentration, and 367 µg/L as the post-breakthrough average in the dietary risk assessment.

Table 5.3.1. Estimated Drinking Water Concentrations of Pymetrozine and Total Toxic Residues

Drinking Water Source	Use Site; Modeled Source	Residue	Application Rate	EDWCs from Pesticide Root Zone Model – Variable Volume Water Model (PRZM-VVWM)		
				1-in-10 Year Concentration (µg/L)		30 Year Annual Average Concentration (µg/L)
				Daily Average	Annual Average	
Surface Water	Outdoor – Christmas trees, Ornamentals, & Fruits (Nonbearing fruit and nut trees in nurseries); Index Reservoir	Pymetrozine	Maximum Use Rate[a]	23	5	3
		TTR		47	13	10
				EDWCs from Pesticide Root Zone Model – Groundwater (PRZM-GW) Concentration (µg/L)		
				Peak	Post-Breakthrough Average	
Groundwater	Outdoor – Christmas trees, Ornamentals, & Fruits (Nonbearing fruit and nut trees in nurseries); Unconfined well	Pymetrozine	Maximum Use Rate[a]	0.09	NA	
		TTR		**404**	**367**	
	Potatoes; Unconfined well	TTR	Typical Use Rate[b]	89	79	

a) Total maximum single use rate from Endeavor and Mainspring Flora product labels: 0.3125 lb a.i./A (0.35 kg/ha) and 5 applications
b) Typical use rate for potatoes: 0.172 lbs a.i./acre (0.193 kg/ha) with 2 applications based on the 90th percentile
NA – Not Applicable due to no breakthrough

In accordance with EFED's recommendation, HED used 404 ppb in the acute assessments and 367 ppb in the chronic assessments. Because the EDWCs resulted in risk estimates of concern, HED requested that EFED provide refined EDWCs. EFED responded by providing EDWCs for scenarios other than the maximum labeled use rate. EFED generated EDWCs for the typical use rate on potatoes (a major use for pymetrozine), the lowest labeled maximum use rate, and the

typical use rate on general vegetables. EFED generated the EDWCs using the Pesticide Root Zone Model-Groundwater (PRZM-GW). These EDWCs are provided in the table below. HED performed cancer dietary exposure assessments based on these EDWCs for food and water and for water only.

Table 5.3.2. Chronic and Cancer EDWCs: Groundwater

EDWC (ppb)	Application Scenario
367	Maximum Use Rate: Post-Breakthrough Average
79	Typical Use Rate on Potatoes
40	Lowest Maximum Use Rate
20	Typical Use Rate on General Vegetables

The drinking water models EFED uses and their descriptions are available at the EPA internet site: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/about-water-exposure-models-used-pesticide.

5.4 Dietary Risk Assessment

HED conducted acute, chronic, and cancer dietary (food and drinking water, drinking water only, and food only) exposure and risk assessments using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). The analyses were conducted in support of a draft human health risk assessment for registration review. This memorandum was reviewed by two peer reviewers of the DESAC, per DESAC Standard Operating Procedure (SOP) 2012.1.

Pymetrozine is registered for use on leafy vegetables (crop groups 4 and 5), fruiting vegetables, cucurbits, tuberous and corm vegetables, and a small number of individual crops. Tolerances have not been established for livestock commodities. HED incorporated the estimated drinking water concentrations (EDWCs) provided by the Environmental Fate and Effects Division (EFD) into the assessments. Pymetrozine is a likely carcinogen, and HED has assigned a cancer potency factor to it. The cancer risk estimates for drinking water alone, and for food plus drinking water exceed 3×10^{-6} when the cancer EDWC recommended by EFED is used. The cancer risk estimate for food only is approximately 7×10^{-7}. The acute and chronic dietary risk estimates are also of concern for the most highly exposed population subgroups when drinking water is included in the assessments. As a refinement, HED performed acute, chronic, and cancer dietary exposure assessments for food alone, drinking water alone, and food plus drinking water. The EDWCs were derived using a total toxic residue approach, and include all degradates of concern in drinking water. The EDWCs were also based on the highest maximum label use rate. EFED provided HED with refined EDWCs based on reduced use patterns or more restricted uses, as discussed above. HED performed cancer dietary exposure assessments using these reduced EDWCs. The results of all of these assessments are reported in this dietary exposure memorandum.

5.4.1 Description of Residue Data Used in Dietary Assessment

Tolerances for pymetrozine are established in 40CFR §180.556. The residue of concern for tolerance enforcement is parent pymetrozine. The residues of concern for risk assessment include parent pymetrozine as well as the following plant metabolites: GS-23199, CGA-215525, CGA-249257, and CGA-294849. The metabolite GS-23199 serves as a marker compound for CGA-215525, CGA-249257, and CGA-294849. As a result, the residue values used in the dietary analyses (acute, chronic, and cancer) include both parent and metabolites of potential risk concern. Residues of GS-23199 were reported in the available field trial data, and ratios based on metabolism studies were used to estimate residue levels for the remaining metabolites of concern (D310560, M. Doherty, 12/29/2004). The residue inputs for food commodities have not changed since the 2004 dietary assessment. For the acute analysis, maximum residues of parent plus metabolites were used, and for the chronic and cancer analyses, average residues of parent plus metabolites were used. For most processed commodities, the residues used in the assessment accounted for concentration or reduction; however, HED used conservative default processing factors for dried potatoes (granules/flakes and flour), dried tomatoes, dried bell peppers, and dried nonball peppers.

5.4.2 Percent Crop Treated Used in Dietary Assessment

Acute Assessment

The acute assessment is based on the assumption that 100% of all commodities with tolerances will be treated with pymetrozine.

Chronic and Cancer Assessments

In the chronic and cancer dietary exposure assessments, HED used the average percent crop treated estimates provided by BEAD in its screening level usage analysis (SLUA) of April 27, 2016.

The following average percent crop treated estimates (SLUA, J. Alsadek, 4/27/2016) were used in the chronic dietary and cancer dietary risk assessment for the following crops that are currently registered for pymetrozine: asparagus: 5%; broccoli: 2.5%; Brussels sprouts: 15%; cabbage: 5%; cantaloupe: 5%; cauliflower: 5%; celery: 20%; cucumber: 2.5%; lettuce, head: 5%; lettuce, leaf: 5%; pecan: 2.5%; pepper: 5%; potato: 5%; pumpkin: 2.5%; spinach: 2.5%; squash: 2.5%; tomato: 5%; watermelon: 2.5%.

5.4.3 Acute, Chronic, and Cancer Dietary Risk Assessment

For acute and chronic assessments, HED is concerned when dietary risk estimates exceed 100% of the PAD. The DEEM-FCID analyses estimate the dietary exposure and risk of the general U.S. population and various population subgroups. The results reported in Tables 5.4.3.1 and 5.4.3.2 are for the general U.S. Population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50-99 years.

Results of Acute Dietary Exposure and Risk Assessments

For food only, the acute dietary risk estimates are not of concern. The general U.S. population uses 27% of the acute population adjusted dose (aPAD) at the 95th percentile of exposure. The most highly exposed population subgroup, Children 1-2 years old uses 45% of the aPAD. Acute dietary risks are of concern when residues in drinking water are included in the dietary exposure assessments. For the assessments that include drinking water only and food plus drinking water, the general U.S. population uses 270% and 290% of the aPAD, respectively. The most highly exposed population subgroup, All Infants, uses 850% of the aPAD for drinking water alone as well as food plus drinking water. The results of the acute dietary exposure assessments are summarized in Table 5.4.3.1, below.

Results of Chronic Dietary (Food Only) Exposure and Risk Assessments

For food only, the chronic dietary risk estimates are not of concern. The general U.S. population and all population subgroups use <1% of the chronic population adjusted dose (cPAD). Chronic dietary risk estimates are of concern for some population subgroups, but not for others, when residues in drinking water are included. The general U.S. population uses 95% of the cPAD when the assessments include drinking water only and food plus drinking water. The most highly exposed population subgroup, All Infants, uses 240% of the cPAD for drinking water alone as well as for food plus drinking water. The results of the chronic dietary exposure assessments are summarized in Table 5.4.3.2, below.

Results of Cancer Dietary Risk Assessments

HED determines cancer risk for the adult subpopulation with the highest exposure estimate. For pymetrozine, that subgroup is Adults 20-49 for all scenarios analyzed. For the assessments that included food and drinking water, cancer risk estimates using the range of EDWCs described in Table 5.3.2 ranged from 5.7 x 10^{-6} (20 ppb EDWC) to 9.2 x 10^{-5} (367 ppb EDWC). For the assessments that included drinking water only, cancer risk estimates ranged from 5.0 x 10^{-6} (20 ppb EDWC) to 9.1 x 10^{-5} (367 ppb EDWC). For food only, the cancer risk estimate is 7.1 x 10^{-7}. The results of the cancer dietary exposure assessments are summarized in Tables 5.4.3.3 and 5.4.3.4, below.

Table 5.4.3.1. Summary of Acute Dietary Exposure and Risk at the 95th Percentile of Exposure EDWC: 404 ppb

Population Subgroup	Food and Drinking Water		Drinking Water Only		Food Only	
	Dietary Exposure (mg/kg/day)	% aPAD 95th %ile	Dietary Exposure (mg/kg/day)	% aPAD 95th %ile	Dietary Exposure (mg/kg/day)	% aPAD 95th %ile
General U.S. Population	0.023161	290	0.022029	270	0.002221	27
All Infants (<1 year old)*	**0.069019**	**850**	**0.068998**	**850**	0.001520	19
Children 1-2 years old*	0.035390	440	0.033969	420	**0.003618**	**45**
Children 3-5 years old	0.029122	360	0.027564	340	0.003520	43
Children 6-12 years old	0.022067	270	0.021061	260	0.002161	27
Youth 13-19 years old	0.018952	230	0.018346	230	0.001772	22
Adults 20-49 years old	0.022704	280	0.021678	270	0.002256	28

Table 5.4.3.1. Summary of Acute Dietary Exposure and Risk at the 95th Percentile of Exposure EDWC: 404 ppb						
Population Subgroup	Food and Drinking Water		Drinking Water Only		Food Only	
	Dietary Exposure (mg/kg/day)	% aPAD 95th %ile	Dietary Exposure (mg/kg/day)	% aPAD 95th %ile	Dietary Exposure (mg/kg/day)	% aPAD 95th %ile
Adults 50-99 years old	0.020428	250	0.019310	240	0.002076	26
Females 13-49 years old	0.023132	290	0.021987	270	0.002207	27

*The subpopulation with the highest exposure estimates.

Table 5.4.3.2. Summary of Chronic Dietary Exposure and Risk for Pymetrozine EDWC: 367 ppb						
Population Subgroup	Food and Drinking Water		Drinking Water Only		Food Only	
	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	% cPAD*
General U.S. Population	0.007727	95	0.007685	95	0.000042	<1
All Infants (<1 year old)	**0.019829**	**240**	**0.019815**	**240**	0.000014	<1
Children 1-2 years old*	0.011112	140	0.011085	140	0.000026	<1
Children 3-5 years old	0.009364	120	0.009340	120	0.000025	<1
Children 6-12 years old	0.006754	83	0.006736	83	0.000018	<1
Youth 13-19 years old	0.005622	69	0.005604	69	0.000018	<1
Adults 20-49 years old	0.007726	95	0.007667	95	**0.000060**	<1
Adults 50-99 years old	0.007618	94	0.007580	94	0.000039	<1
Females 13-49 years old	0.007670	95	0.007639	94	0.000032	<1

*The subpopulation with the highest exposure estimates.

Table 5.4.3.3. Cancer Dietary Risk Estimates for Food and Drinking Water		
Adult Subgroup with Highest Risk Estimate	EDWC (ppb)	Cancer Risk Estimate
Adults 20-49	367	9.2×10^{-5}
Adults 20-49	79	2.0×10^{-5}
Adults 20-49	40	1.1×10^{-5}
Adults 20-49	20	5.7×10^{-6}

Table 5.4.3.4. Cancer Dietary Risk Estimates for Drinking Water Only		
Adult Subgroup with Highest Risk Estimate	EDWC (ppb)	Cancer Risk Estimate
Adults 20-49	367	9.1×10^{-5}
Adults 20-49	79	2.0×10^{-5}
Adults 20-49	40	9.9×10^{-6}
Adults 20-49	20	5.0×10^{-6}

Contribution of Residues in Drinking Water

In the acute, chronic, and cancer dietary exposure assessments, residues in drinking water were the primary contributor to dietary exposure and risk. In the acute assessment, the most highly

exposed population subgroup, All Infants, used 850% of the aPAD when residues in drinking water were included, regardless of whether or not residues in food were included. This same population subgroup used 19% of the aPAD when residues in food only were included. In the chronic assessment, the most highly exposed population subgroup, All Infants, used 240% of the cPAD when residues in drinking water were included, regardless of whether or not residues in food were included. This same population subgroup used <1% of the cPAD when residues in food only were included. In the cancer assessment, the risk estimate is 7.1×10^{-7} when residues in food only are included. When residues in drinking water are included, as the EDWCs increase from 20 ppb to 367 ppb, the risk estimates increase from 5.0×10^{-6} to 9.1×10^{-5}.

6.0. Residential (Non-Occupational) Exposure/Risk Characterization

6.1 Residential Handler Exposure and Risk Estimates

All registered pymetrozine product labels with residential use sites (e.g., garden and trees) require that handlers wear specific clothing (e.g., long sleeve shirt/long pants) and PPE (e.g., gloves). Therefore, HED has made the assumption that these products are not for homeowner use, and has not conducted a quantitative residential handler assessment.

6.2 Residential Post-application Exposure and Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that was previously treated with pymetrozine. The quantitative risk assessment for residential post-application exposures is based on the 2012 Residential SOP: Gardens and Trees.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[4]. While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Post-application Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs[4].

Application Rate: The application rates for the registered uses of pymetrozine can be found in Appendix E of this draft risk assessment.

Exposure Duration: Residential post-application exposure is expected to be short-term in duration. Intermediate-term exposures are not likely because of the intermittent nature of applications to residential areas.

[4] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Dislodgeable Foliar Residues: Data have been submitted and reviewed by HED for the dissipation of dislodgeable foliar residues of pymetrozine from rose foliage grown in greenhouses (D444609, G. Thornton, 12/14/2017). As the study was conducted only for 24-hours indoors, it is difficult to determine the actual dissipation of the product on ornamentals. Since there are fewer environmental factors (e.g., wind, rain, etc.) that would facilitate foliar dissipation in indoor areas (e.g., greenhouses) as well as the short duration of the study, HED is confident that the predicted dissipation of product on ornamentals does not underestimate the real dissipation. Additionally, no risk estimates of concern were identified assuming Day 0 predicted DFR. A summary of the DFR study analysis is shown below in Table 6.2. A full summary of the DFR study is available in Appendix D of the Occupational and Residential Exposure (ORE) Memorandum prepared in support of this draft risk assessment for registration review (D444128, G. Thornton, 12/14/2017).

Table 6.2.. Summary of Pymetrozine DFR (Rose) Study Analysis.

Crop	Location	Field Fortification Recoveries	Application Rate	R^2	Half Life	Maximum Predicted 0 DAT DFR
	States	%	(lb ai/acre)		days	µg/cm^2
Greenhouse (Rose)	Creedmoor, North Carolina	Low level (≤ 0.995 µg/cm^2): 88.5 High level (>0.995 µg/cm^2): 94.9	0.345	0.2353[1]	9.9	0.668

Body Weight: Since the dermal and inhalation PODs are based on developmental and/or fetal effects, the body weight appropriate for adult dermal and inhalation assessments is 69 kg. A body weight of 32 kg was used for children (6 to <11 years old) dermal assessment. A body weight of 80 kg was used for the cancer assessment.

Residential Post-application Non-cancer Exposure and Risk Equations

The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs[5] as well as in Appendix A of the ORE memo prepared in support of this draft risk assessment (D444128, G. Thornton, 12/14/2017).

Combining Exposure and Risk Estimates

While all routes of exposure are based on the same study and therefore should be combined, only post-application dermal exposure is expected from the registered uses (i.e., exposure to treated gardens/trees); and therefore, it is not applicable to combine dermal exposure with any other routes of exposure.

Summary of Residential Post-application Non-cancer Exposure and Risk Estimates

There are no risks of concern from post-application exposure from gardens/trees treated with pymetrozine-containing products. Dermal MOEs range from 4,100 to 340,000 for adults and 6,900 to 590,000 for children (6 to <11 years old). The summary of the residential post-application non-cancer risk estimates is presented in Appendix E the ORE memorandum

[5] http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

(D444128, G. Thornton, 12/14/2017), an Excel spreadsheet titled, *D444128_Appendix E Residential Post-application Gardens_Trees Non_Cancer Risks (Postapp Dermal_with DFR).*

Residential Post-application Cancer Exposure and Risk Estimate Equations

Post-application cancer risk estimates for adults were calculated using a linear low-dose extrapolation approach in which a Lifetime Average Daily Dose (LADD) is first calculated and then compared with a cancer slope factor (Q_1*) that has been calculated for pymetrozine based on dose response data in the appropriate toxicology study (Q_1* = 0.0119 $(mg/kg/day)^{-1}$). The algorithms used to estimate the LADD and cancer risk for residential post-application exposure can be found in Appendix B of the ORE memorandum (D444128, G. Thornton, 12/14/2017). The inputs for the post-application cancer calculations are highlighted below.

Deposited Residues & Dermal Dose Estimates

To determine the average dermal dose over the course of a year, HED combined the starting pymetrozine depositions (deposited foliar residue) identified for each scenario in Table 6.2.1 and input a daily dissipation each day until the next application took place. The following assumptions were incorporated into the assessment:

- A chemical specific DFR dissipation (i.e., 7% from the greenhouse study) rate was used for exposures from treated gardens/trees.
- Retreatment intervals (RTIs) of 7 and 14 days were considered, however, the deposited residue estimates were found to be relatively similar between the two RTIs.
- A dermal absorption factor of 1% was used to determine all dermal cancer estimates assessed.
- The product may be applied less than 5 times in one year outdoors (maximum single application rate of 0.313 lb ai/A; maximum yearly application rate of 1.5 lb ai/A) and up to 10 times in one year indoors (maximum single application rate of 0.313 lb ai/A; maximum yearly application rate of 3.13 lb ai/A).

Days Per Year of Exposure: Exposure to treated gardens and trees is expected to result in 120 days of exposure per year (4 months of exposure during warm weather/summer). It is also expected that exposure to indoor plants (e.g., pruning, watering, etc.) would not typically occur more than twice per week, resulting in 104 days of exposure per year.

Years Per Lifetime of Exposure: It is assumed that adults would be exposed for 50 years out of a 78-year lifespan.

Summary of Residential Post-application Cancer Exposure and Risk Estimates

Dermal cancer risk estimates range from 9.2×10^{-7} to 1.95×10^{-8} from exposure to treated gardens and trees. The summary of the residential post-application cancer risks is presented in Appendix E of the ORE memorandum (D444128, G. Thornton, 12/14/2017), and in an Excel spreadsheet titled, *D444128_Appendix E Residential Post-application Gardens_Trees Cancer Risks* and *D444128_Appendix E Residential Post-application Indoor_Plants Cancer Risks (Postapp Dermal_with DFR).*

6.3 Residential Risk Estimates for Use in Aggregate Assessment

Tables 6.3.1 (non-cancer) and 6.3.2 (cancer) reflect the residential risk estimates that are recommended for use in the aggregate assessment for pymetrozine. Shaded numbers are considered in the aggregate assessment.

- The recommended residential exposure for use in the adult non-cancer aggregate assessment reflects dermal exposure from post-application activities in gardens.
- The recommended residential exposure for use in the children 6 to <11 years old non-cancer aggregate assessment reflects dermal exposures from post-application activities in gardens.
- The recommended residential exposure for use in the cancer aggregate assessment reflects dermal exposure from post-application activities in gardens.

Table 6.3.1. Recommendations for the Residential Exposures for the Pymetrozine Non-cancer Aggregate Assessment.

Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Adult	Gardens	0.001975	N/A		0.001975	4,100	N/A		4,100
Children (6 to <11 years)	Gardens	0.001166	N/A		0.001166	6,900	N/A		6,900

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).

2 MOE = the MOEs associated with the highest residential doses. Total = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental Oral MOE), where applicable.

Table 6.3.2. Recommendations for the Residential Exposures for the Pymetrozine Cancer Aggregate Assessment.

Lifestage	Exposure Scenario	Lifetime Average Daily Dose (mg/kg/day)[1]				Cancer Risk Estimate[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Adult	Gardens	7.73E-05	N/A		7.73E-05	9.20E-07	N/A		9.20E-07

1 Dermal LADD (mg/kg/day) = Dermal dose (mg/kg/day) × [120 (days/yr) ÷ 365 days/year] × [50 (yrs) ÷ 78 (yrs)]. Total LADD (mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).

2 Cancer risk estimates = Total LADD × Q_1^*, where $Q_1^* = 0.0119$ $(mg/kg/day)^{-1}$.

6.4 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (e.g., children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[6] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift, thus resulting in an indirect exposure are the focus of this analysis, analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of norflurazon. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs)*.
A screening approach was developed based on the use of the AgDrift model in situations where specific label guidance that defines application parameters is not available.[7] AgDrift is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). Section 6.1 summarizes the screening level drift related risk estimates. Appendix E of this document presents the spray drift algorithms used for risk assessment.

For pymetrozine, chemical-specific turf transferable residues (TTR) data are not available, therefore, the estimated TTR are based on a default assumption from the 2012 Residential SOPs that the transferable residue available for exposure is 1% of the total deposited residue.

6.5 Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a

[6] This approach is consistent with the requirements of the EPA's Worker Protection Standard.
[7] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#AgDrift

result of the screening level agricultural application scenarios. Pymetrozine is used on various agricultural crops and can be applied via groundboom, airblast, and aerial application equipment. The algorithms and assumptions used in this spray drift assessment can be found in Appendix C of the ORE memorandum (D444128, G. Thornton, 12/14/2017). The recommended drift scenario screening level options are listed below:

- Groundboom applications are based on the AgDrift option for high boom height and using very fine to fine spray type using the 90th percentile results.
- Orchard airblast applications are based on the AgDrift option for Sparse (Young/Dormant) tree canopies.
- Aerial applications are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters that will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).[8]

Summary of Spray Drift Exposure and Risk Estimates

Results of the non-occupational spray drift risk assessment for pymetrozine are presented in Appendix E of the ORE memorandum (D444128, G. Thornton, 12/14/2017) in the Excel spreadsheet, *D444128_Appendix E_ Spray Drift Risks.* The adult spray drift risk summary is presented on the *Adult Buffer Summary* tab, and children 1 to < 2-year-old summary is presented on the *1<2 Combined Buffer Summary* tab. Exposures were considered for 50 feet wide lawns where the nearest side of the property was directly adjoining the treated field (at field edge).

Adult dermal and children's (1 to <2 years old) combined dermal and incidental oral risk estimates from indirect exposure to pymetrozine are not of concern for lawns adjacent to the edge of the field. Dermal MOEs for adults range from an MOE of 23,000 to 41,000 and combined dermal and incidental oral MOEs for children (1 to <2 years old) range from an MOE of 4,400 to 8,000. Dermal and incidental oral risk estimates were combined for children 1 to <2 years old because the toxicity endpoint for each route of exposure is the same, morphometric changes in the brains of female pups on PND 12 and male pups on PND 63 from the DNT.

6.6 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/docket?D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for pymetrozine.

[8] AgDrift allows for consideration of even finer spray patterns characterized as very fine to fine. However, this spray pattern was not selected as the common screening basis since it is used less commonly for most agriculture.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risk estimates from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risk estimates themselves can be aggregated. When aggregating exposure and risk from various sources, HED considers both the route and duration of exposure.

7.1 Acute Aggregate Risk

Acute aggregate risk from exposure to pymetrozine results from exposure to residues in food and drinking water alone. The acute dietary exposure analysis included both food and drinking water; therefore, acute aggregate risk estimates are equivalent to the acute dietary risk estimates, as discussed in Section 5.4.3, above. Acute aggregate risk is of concern for the general U.S. population and all population subgroups.

7.2 Short-Term Aggregate Risk Estimates

Short-term aggregate risk assessments are needed for adults and children 6 to less than 11 years old, and include exposure through the dietary and dermal routes. The dermal endpoint is based on neurotoxic effects seen in the rat developmental neurotoxicity study. Morphometric changes were seen in the brains of female pups on PND 12 and male rat pups on PND 63. In accordance with the FQPA, the dermal exposure is added to the background dietary exposure from the chronic dietary exposure assessment.

For both adults and children 6 to less than 11, dermal exposure results from post-application contact with residues in treated gardens. For the short-term aggregate assessment, the dermal exposure was added to the chronic dietary exposure to arrive at the aggregate exposure. The combined MOE's were calculated and compared to the LOC of 1,000.

For the cancer aggregate assessment, dermal exposure also results from post-application contact with residues in treated gardens. The dermal exposure was added to the background dietary exposure for the adult population subgroup with the highest exposure, Adults 20-49.

Short-term aggregate risk is not of concern for children 6-<11 years of age. However, the aggregate MOE for adults is 830, which is below the LOC of 1,000.

As discussed in Section 5.4.3, above, the cancer dietary risk estimate for Adults 20-49 exceeds 1 x 10^{-6}. When the residential exposure is combined with the background dietary exposure, the cancer risk estimate increases from 9.2 x 10^{-5} to 9.3 x 10^{-5}.

Table 7.2.1. Short-Term Aggregate Risk Calculations for Adults and Children 6-<11 Years Old							
Scenario	Short- or Intermediate-Term Scenario						
	POD mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day[4]	Aggregate MOE (food, water, and residential)[5]
Adults: Gardens	8.1	1,000	0.0081	0.007726	0.001975	0.009701	**830**
Children 6-<11: Gardens	8.1	1,000	0.0081	0.006754	0.001166	0.007920	**1.0×10^3**

[1] LOC is based on a 10x interspecies UF, a 10x intraspecies UF, and a 10x FQPA Safety Factor
[2] Maximum Allowable Exposure (mg/kg/day) = POD/LOC
[3] Residential Exposure = Dermal Exposure. See Table 6.3.1 for residential exposure values.
[4] Total Exposure = Avg Food & Water Exposure + Residential Exposure
[5] Aggregate MOE = [LOAEL ÷ (Avg Food & Water Exposure + Residential Exposure)]

Table 7.2.2. Aggregate Cancer Risk Estimates				
Population	Cancer Slope Factor (Q_1*)	Food and Water Exposure (mg/kg/day)	Residential Exposure (LADD)[1] (mg/kg/day)[2]	Aggregate Cancer Risk (food, water, residential)[3]
Adults 20-49	0.0119	0.007726	0.0000773	9.3×10^{-5}

[1] LADD: Lifetime average daily dose
[2] Residential Exposure = Dermal exposure resulting from garden treatment. See Table 6.3.1 for residential exposure value.
[3] Aggregate Cancer Risk = (Q_1*) (Food & Water Exposure + LADD)

8.0 Cumulative Exposure and Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to pymetrozine and any other substances and pymetrozine does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that pymetrozine has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document titled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[9] and conducting cumulative risk assessments (CRA)[10]. During registration review, the Agency will utilize this framework to determine if the available toxicological data for pymetrozine suggests a candidate CMG may be established with

[9] Guid*ance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)
[10] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

9.0 Occupational Exposure and Risk Characterization

9.1 Occupational Handler Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the registered uses of pymetrozine. The quantitative exposure/risk assessment developed for occupational handlers is based on all registered uses of pymetrozine; the exposure scenarios are in the *OccHndler_Non-cancer* tab in the Excel spreadsheet, *D444128_Appendix E_ Occupational Handler Non-cancer Risks* found in Appendix E (D444128, G. Thornton, 12/14/2017).

Occupational Handler Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

Application Rate: A summary of the registered application rates is presented in Appendix E of this memorandum.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, and the AHETF database. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures," are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[11]," which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[12].

Area Treated or Amount Handled: The area treated/amounts handled are summarized in Appendix E of the ORE memorandum (D444128, G. Thornton, 12/14/2017), an Excel spreadsheet titled, *D444128_Appendix E_ Occupational Handler Non-cancer Risks.* The assumptions are based on guidance in the ExpoSAC Policy 9.1.

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things,

[11] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data
[12] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region). For pymetrozine, based on the registered uses, short- and intermediate-term exposures are expected. However, the dermal and inhalation PODs are the same for both durations; therefore, the assessment is applicable to both short- and intermediate-term exposures.

Body Weight: Since the dermal and inhalation PODs are based on developmental and/or fetal effects, the body weight appropriate for the adult non-cancer dermal and inhalation assessment is 69 kg. A body weight of 80 kg was used for the cancer assessment.

Personal Protective Equipment: Estimates of dermal and inhalation exposure were calculated for various levels of personal protective equipment (PPE). Results are presented starting at the lowest level of PPE required on all registered labels: "baseline," attire (a long sleeved shirt, long pants, shoes plus socks), chemical resistant gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., gloves and respirator) or engineering controls (aerial applicator only).

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix A of the ORE memorandum (D444128, G. Thornton, 12/14/2017).

Combining Exposures/Risk Estimates

Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes were the same. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = Point of Departure (mg/kg/day) ÷ Combined dermal + inhalation dose (mg/kg/day)

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

With two exceptions, there are no occupational handler combined risk estimates of concern (i.e., total MOE), with total MOEs ranging from 1,100 to 1,100,000 (LOC = 1,000). Using label specified clothing and PPE (i.e., baseline attire and gloves), mixing/loading WDG formulated products for aerial application on field crops (high/typical acreage) and mixing/loading WDG formulated products for chemigation on field crops (high/typical acreage) have total MOEs less than the LOC of 1,000, with MOEs ranging from 280 to 950. Inhalation exposure is driving the combined risk estimate. With the addition of a PF5 respirator, the MOEs are no longer of concern:

- MOE = 1,200 for mixing/loading WDG for aerial applications on field crops (high acreage); and
- MOE = 4,000 for mixing/loading WDG for aerial application on field crops (typical acreage) and chemigation of field crops (high/typical acreage).

The occupational handler exposures and risk estimates are summarized in Appendix E of the ORE memorandum (D444128, G. Thornton, 12/14/2017), an Excel spreadsheet titled, *D444128_Appendix E_ Occupational Handler Non-cancer Risks.*

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

HED has no data to assess exposures to pilots using open cockpits. The only data available are for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective chemical resistant gloves for the duration of the application. With this level of protection, there are no risk estimates of concern for applicators.

Occupational Handler Cancer Exposure and Risk Equations

Cancer risk estimates were calculated using a linear low-dose extrapolation approach in which a Lifetime Average Daily Dose (LADD) is first calculated and then compared with a Q_1* that has been calculated for pymetrozine based on dose response data in the appropriate toxicology study (Q_1* = 0.0119 $(mg/kg/day)^{-1}$). Absorbed average daily dose (ADD) levels were used as the basis for calculating the LADD values. Dermal and inhalation ADD values were first added together to obtain combined ADD values. LADD values were then calculated and compared to the Q_1* to obtain cancer risk estimates. The algorithms used to estimate the LADD and cancer risk for occupational handlers can be found in Appendix B of the ORE memorandum (D444128, G. Thornton, 12/14/2017).

Days per Year of Exposure: To assess cancer risk (both agricultural and non-agricultural uses), it is assumed that private growers would be exposed 10 days per year and commercial applicators would be exposed 30 days per year. The term "private grower" means that the grower or one of the workers would apply the pesticides to land owned or operated by the grower. "Commercial applicators" means the applicators are completing multiple applications for multiple clients.

Years per Lifetime of Exposure: It is assumed that handlers would be exposed for 35 years out of a 78-year lifespan.

Lifetime Expectancy: Life expectancy values are from the Exposure Factors Handbook 2011 Edition Table 18-1 (U.S. EPA, 2011). The table shows that the overall life expectancy is 78 years based on life expectancy data from 2007. In 2007, the average life expectancy for males

was 75 years and 80 years for females. Based on the available data, the recommended value for use in cancer risk assessments is 78 years.

Summary of Occupational Handler Cancer Exposure and Risk Estimates

The occupational handler cancer risk estimates for the registered uses of pymetrozine ranged from 7×10^{-9} to 4×10^{-6} for private growers (10 days of exposure/year) and 2×10^{-8} to 1×10^{-5} for commercial applicators (30 days of exposure/year), assuming label specified clothing and PPE (i.e., baseline attire and gloves). The occupational handler exposures and cancer risk estimates are summarized in Appendix E of the ORE memorandum (D444128, G. Thornton, 12/14/2017), an Excel spreadsheet titled, *D444128_Appendix E_ Occupational Handler Cancer Risks (OccHndler_Cancer tab).*

9.2 Occupational Post-Application Exposure/Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures might occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

9.2.1 Occupational Post-Application Inhalation Exposure/Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/docket?D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for pymetrozine.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the agency's risk assessments.

9.2.2 Occupational Post-Application Dermal Exposure/Risk Estimates

Occupational Post-application Dermal Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessments. Each assumption and factor is detailed below on an individual basis.

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region). For pymetrozine, based on the registered uses, short- and intermediate-term exposures are expected. However, the dermal and inhalation PODs are the same for both durations; therefore, the assessment is applicable to both short- and intermediate-term exposures.

Transfer Coefficients: It is the policy of HED to use the best available data to assess post-application exposure. Sources of generic post-application data, used as surrogate data in the absence of chemical-specific data, are derived from ARTF exposure monitoring studies, and, as proprietary data, are subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting post-application exposure that are used in this assessment, known as "transfer coefficients", are presented in the ExpoSAC Policy 3[13]" which, along with additional information about the ARTF data, can be found at the Agency website[14].

Application Rate: A summary of the registered application rates is presented in Appendix E of this memorandum.

Exposure Time: The average occupational workday is assumed to be 8 hours.

Dislodgeable Foliar Residues: Data have been submitted and reviewed by HED for the dissipation of dislodgeable foliar residues of pymetrozine from rose foliage grown in greenhouses (D444609, G. Thornton, 12/14/2017) and on lettuce (D444608, G. Thornton, 12/14/2017). A summary of the DFR studies analyses is shown below in Table 9.2.2. For a full summary of the DFR studies, please see Appendix D of the ORE memorandum (D444128, G. Thornton, 12/14/2017).

All post-application activities that take place in ornamental plants (e.g., floriculture crops, nursery crops, etc.) were assessed using the rose DFR data. All other crops were assessed using the lettuce DFR data from the Arizona site.

[13] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data
[14] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

Table 9.2.2. Summary of Pymetrozine DFR Studies Analyses.							
Crop	**MRID No.**	**Site**	**Field Fortification Recoveries**	**Application Rate**	**R^2**	**Half Life**	**Maximum Predicted DFR[1]**
		States	**%**	**(lb ai/acre)**		**days**	**µg/cm²**
Greenhouse (Roses)[1]	44411319	Creedmoor, North Carolina	Low level (≤ 0.995 µg/cm²): 88.5 High level (>0.995 µg/cm²): 94.9	0.345	0.2353	9.9	0.668 0 DAT
Lettuce	45387805	Yuma, Arizona	Low level (≤ 0.210 µg/cm²): 60.9 High level (>0.210 µg/cm²): 72.9	0.0892	0.9868	1.2	0.149 0 DAT
		Madera, California	Low level (≤ 0.210 µg/cm²): 99.1 High level (>0.210 µg/cm²): 96.9		0.7612	2.1	0.142 0 DAT

[1] As the study was conducted only for 24-hours indoors, it is difficult to determine the actual dissipation of the product on ornamentals. Since there are fewer environmental factors (e.g., wind, rain, etc.) that would facilitate foliar dissipation in indoor areas (e.g., greenhouses) as well as the short duration of the study, HED is confident that the predicted dissipation of product on ornamentals does not under estimate the real dissipation. Additionally, no risk estimates of concern were identified assuming Day 0 predicted DFR.

Dislodgeable Boll Residues: Chemical-specific dislodgeable boll residue data have not been submitted for pymetrozine. Therefore, this assessment uses HED's default assumption that 2x the application is available for transfer on day 0 following the application, and that the residues dissipate at a rate of 10% each following day.

Occupational Post-application Non-cancer Dermal Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational post-application workers can be found in Appendix A of the ORE memorandum (D444128, G. Thornton, 12/14/2017).

Summary of Occupational Post-application Non-cancer Dermal Risk Estimates

There are no occupational post-application dermal risks of concern on the day of application (Day 0) for activities and crops/use sites assessed, with dermal MOEs ranging from 2,400 to 690,000 (LOC = 1000). The summary of the anticipated post-application activities and associated transfer coefficients for the registered crops/use sites is summarized in Appendix E of the ORE memorandum (D444128, G. Thornton, 12/14/2017), in two Excel spreadsheets titled, *D444128_Appendix E_Occupational Post-Application Non-cancer Risks Crops* and *D444128_Appendix E_Occupational Post-Application Non-cancer Risks Ornamentals* (*Occup Expo-Risk-REI Calculator* tab).

Restricted Entry Interval

Pymetrozine is classified as Toxicity Category III via the dermal route as well as for eye irritation, and Toxicity Category IV for skin irritation potential. It is a slight dermal sensitizer. Short- and intermediate-term post-application risk estimates were not a concern on day 0 (12

hours following application) for all post-application activities. Under 40 CFR 156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to pymetrozine. HED would recommend a REI of 12 hours. This is the REI listed on the registered agricultural labels, and is considered protective of post-application exposure.

Occupational Post-application Cancer Dermal Exposure and Risk Equations

As was done for occupational handlers, post-application cancer risk estimates were calculated using a linear low-dose extrapolation approach in which a LADD is first calculated and then compared with a Q_1^* that has been calculated for pymetrozine based on dose response data in the appropriate toxicology study ($Q_1^* = 0.0119$ (mg/kg/day)$^{-1}$). The algorithms used to estimate the LADD and cancer risk for occupational workers can be found in Appendix B of the ORE memorandum (D444128, G. Thornton, 12/14/2017).

Days per Year of Exposure: To assess cancer risk, it is assumed that post-application scenarios could occur approximately 30 days a year at a 30-day average dose to calculate post-application risk estimates (D429731, B. Bobowiec, 10/16/2015).

Years per Lifetime of Exposure: HED assumes that post-application workers would be exposed for 35 years out of a 78 year lifespan.

Lifetime Expectancy: Based on available data from EPA's Exposure Factors Handbook 2011 Edition, the recommended lifespan for use in cancer risk assessments is 78 years. Life expectancy values are derived from the Exposure Factors Handbook 2011 Edition Table 18-1 (U.S. EPA, 2011). The table shows that the overall life expectancy is 78 years based on life expectancy data from 2007. In 2007, the average life expectancy for males was 75 years and 80 years for females.

Summary of Occupational Post-application Cancer Dermal Risk Estimates

The occupational post-application cancer risk estimates for the registered uses of pymetrozine ranged from 5×10^{-7} to 3×10^{-10} for all activities and crops/use sites. The occupational post-application exposures and cancer risk estimates are summarized in Appendix E of the ORE memorandum (D444128, G. Thornton, 12/14/2017), in two Excel spreadsheets titled, *D444128_Appendix E_ Occupational Post-application Cancer Risks Ornamentals* and *D444128_Appendix E_ Occupational Post-application Cancer Risks Crops* (*Expo-Risk-REI Calculator* tab).

10.0 Public Health and Pesticide Epidemiology Data

In support of this draft human health risk assessment for registration review, HED prepared a report of the incidents and epidemiology associated with pymetrozine (D441356, E. Evans and S. Recore, 7/25/2017). Pymetrozine incidents were previously reviewed in 2013 (E. Evans and S. Recore, D408569, 2/5/2013). At that time, based on the low severity and frequency of cases

reported to both IDS and SENSOR-Pesticides, there was not a risk of concern that warranted further analysis.

In the current IDS analysis from January 1, 2012 to June 7, 2017, no incidents were reported to Main IDS involving pymetrozine; there was one incident reported to Aggregate IDS. A query of SENSOR-Pesticides 1998-2013 identified five cases involving pymetrozine. The AHS is a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA. Pymetrozine is not included in the AHS, and therefore this study does not provide information for this report.

Based on the continued low frequency of pymetrozine incidents reported to both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time. The Agency will continue to monitor the incident data and if a concern is triggered, additional analysis will be conducted.

11.0 References

D371299, Pymetrozine. Updated Aggregate Human Health Risk Assessment., C. Swartz, E. Scollon, 4/2/2010

D408387, Pymetrozine. Human Health Assessment Scoping Document in Support of Registration Review, D. Dotson, et al, 5/7/2013

TXR # 0056567, Pymetrozine: Summary of Hazard and Science Policy Council (HASPOC) Meeting on January 23, 2013: Recommendations on Data Requirements for a Subchronic Inhalation Study, J. VanAlstine, 3/20/2013

TXR # 0056921, Pymetrozine: Summary of Hazard and Science Policy Council (HASPOC): Recommendations on Data Requirements for an Immunotoxicity Study, K. Rury, 3/27/2014.

TXR # 0014036, Revised Pymetrozine Quantitative Risk Assessment (Q_1*) Based on Tif:RAf(SPF) Sprague-Dawley Rate and TIF:MAGf(SPF) Mouse Chronic Dietary Studies with ¾'s Interspecies Scaling Factor, L. Brunsman, 3/9/2000.

D444490, Pymetrozine Acute, Chronic, and Cancer Dietary Exposure and Risk Assessments in Support of the Registration Review Risk Assessment, D. Dotson, 12/14/2017

D250386, PP#s 8F4984, 8F5031, and 0F6141. Tolerance Petitions for the Use of Pymetrozine on Cotton, Hops, Pecans, Leafy Vegetables (Except Brassica Vegetables), Head and Stem Brassica, Leafy Brassica Greens, Turnip Greens, Cucurbits, and Fruiting Vegetables. Evaluation of Residue Chemistry and Analytical Methodology, D. Dotson, 11/19/2001

D444128, Pymetrozine: Occupational and Residential Exposure and Risk Assessment in Support of Registration Review, G. Thornton, 12/14/2017

D444608, Pymetrozine. Secondary Review of the Determination of Dislodgeable Foliar Residues on Treated Lettuce, G. Thornton, 12/14/2017.

D444609, Pymetrozine. Secondary Review of the Determination of Dislodgeable Foliar Residues on Treated Greenhouse Ornamentals (Roses), G. Thornton, 12/14/2017.

D441356, Pymetrozine: Tier I Update Review of Human Incidents and Epidemiology for Draft Risk Assessment, E. Evans and S. Recore, 7/25/2017

Appendix A. Toxicology Profile

A.1 Toxicology Data Requirements

Table A.1. Toxicology Data Requirements for Conventional Pesticides (Food Use): Pymetrozine

Study	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21/28-Day Dermal	no	yes
870.3250 90-Day Dermal	yes	no[1]
870.3465 90-Day Inhalation	no[2]	---
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	no	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395 Mutagenicity—Mammalian Erythrocyte Micronucleus	no	yes
870.5550 Mutagenicity—Unscheduled DNA Synthesis	no	yes
870.5915 Mutagenicity—*In Vivo* Sister Chromatid Exchange	no	---
870.6100a Acute Delayed Neurotox. (hen)	no	---
870.6100b 90-Day Neurotoxicity (hen)	no	---
870.6200a Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b 90 Day Neurotox. Screening Battery (rat)	yes	yes
870.6300 Develop. Neuro	yes	yes
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	yes
870.7800 Immunotoxicity	no[3]	---

[1] Requirement fulfilled by 21/28 day study.
[2] HASPOC determined that the study was not required (TXR# 0056567)
[3] HASPOC determined that the study was not required (TXR# 0056921)

A.2. Toxicity Profile Tables

Table A.2.1. Acute Toxicity Profile – Pymetrozine Technical				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral – Rat	44024926	LD_{50} > 5955 mg/kg	IV
870.1200	Acute dermal – Rat	44024928	LD_{50} > 2 g/kg	III
870.1300	Acute inhalation – Rat	44024930	LC_{50} > 1.8 mg/L	IV
870.2400	Acute eye irritation - Rabbit	44024932	Minimally irritating	III
870.2500	Acute dermal irritation - Rabbit	44024934	Non-irritating	IV
870.2600	Skin sensitization – Guinea Pig	44024936	Slight dermal sensitizer	---

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile – Pymetrozine		
Study Type	**MRID No.**	**Results**
870.3100 Subchronic Feeding (rats)	44024939 (1992) Acceptable/Guideline 0, 50, 500, 5000 ppm (0/0, 3.4/3.6, 32.5/33.9, 360/370 mg/kg/day [M/F])	LOAEL = 360/370 mg/kg/day based primarily on decreased body weight and liver effects (increased weight and centrilobular hypertrophy in males). Other effects included leukocytosis, bilirubinuria (females) and decreased urine volume (males), increased relative liver and spleen weights, calcification of kidneys (males), and atrophy of the thymus in both sexes. NOAEL = 32.5/33.9 mg/kg/day
870.3100 Subchronic Feeding (Mouse - Dose range-finding study)	44024938 (1992) Acceptable/Non-guideline 0, 1000, 3000, 7000 ppm (0, 143, 429, 1002 mg/kg/day)	LOAEL (males & females) = 143 mg/kg/day (LDT) based on increased liver weight and increased focal cell necrosis in hepatic parenchyma NOAEL (males & females) = Not established
870.3151 Subchronic Feeding (Beagle dogs)	44572201 (1992) Acceptable/Guideline 0, 100, 500, 2500 ppm (0, 3.1, 14, 54 mg/kg/day)	LOAEL = 14 mg/kg/day based on liver pathology (bile duct proliferation in both sexes and hepatocyte necrosis in females), skeletal muscle atrophy, and lymphocytic infiltration in several organs. NOAEL = 3.12 mg/kg/day
870.3200 28-Day Dermal Toxicity (Sprague-Dawley rats)	44024942 (1993) Acceptable/Guideline: 0, 10, 100, 1000 mg/kg/day (6 hrs/day, 5 days/week for 4 weeks)	**Systemic/Dermal Irritation:** LOAEL > 1000 mg/kg/day (HDT) NOAEL = 1000 mg/kg/day

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile – Pymetrozine		
Study Type	**MRID No.**	**Results**
870.3700 Developmental Toxicity (Sprague-Dawley rat)	44024948 (1992) Acceptable/Guideline: 0, 30, 100, 300 mg/kg	**Maternal:** LOAEL = Not established NOAEL = 300 mg/kg/day (HDT) **Developmental:** LOAEL = 300 mg/kg/day based on increased skeletal anomalies including delayed ossification of digits and dumbbell shaped thoracic vertebral centers NOAEL = 100 mg/kg/day
870.3700 Developmental Toxicity (Russian rabbits)	44024949 (1992) Acceptable/Guideline 0, 10, 75, 125 mg/kg	**Maternal:** LOAEL = Not established NOAEL = 125 mg/kg/day (HDT) **Developmental:** LOAEL = 75 mg/kg/day based on skeletal anomalies including increased incidences of 13th ribs, fused sternebrae, and delayed ossification of digits NOAEL = 10 mg/kg/day
870.3800 Reproductive Toxicity (Sprague-Dawley rat)	44024950 (1993) Acceptable/Guideline 0, 20, 200, 2000 ppm (0/0, 1.4/1.6, 13.9/16.0, 136.9/151.6 mg/kg/day [M/F])	**Parental /Systemic:** LOAEL = 136.9/151.6 mg/kg/day based on decreased body weight, decreased body weight gain, decreased food consumption, and liver effects (increased liver weight and minimal hepatocellular hypertrophy) NOAEL = 13.9/16.0 mg/kg/day **Offspring:** LOAEL = 136.9/151.6 mg/kg/day based on decreased pup weight and delay in eye opening on both F1 and F2 litters NOAEL = 13.9/16.0 mg/kg/day **Reproductive**: LOAEL ≥ 136.9/151.6 mg/kg/day NOAEL > 136.9/151.6 mg/kg/day
870.4100 Chronic Feeding (beagle dog)	44024943 (1994) Acceptable/Guideline 0, 20, 200, 1000 ppm (0, 0.57, 5.33, 27.8 mg/kg/day)	LOAEL = 27.8 mg/kg/day based primarily on myopathy and anemia. Additional effects included inflammatory cell infiltration in the liver (males), cholesterol, phospholipids, hemosiderosis, decreased testis weight and increased liver weight. NOAEL = 5.33 mg/kg/day. An equivocal increase in liver weight at 5.33 mg/kg/day did not show related pathology or dose response and was considered adaptive and not adverse.
870.4200 Carcinogenicity (mouse)	44024944 (1995) Acceptable/Guideline: 0, 10, 100, 2000, 5000 ppm (0, 1.2, 12, 250, 675 mg/kg/day)	LOAEL = 250 mg/kg/day based on liver weight and hepatocyte hypertrophy, hemosiderosis and extramedullary hematopoiesis NOAEL = 12 mg/kg/day At ≥ 250 mg/kg/day, increased incidences of benign liver hepatomas and/or carcinomas combined in both sexes.
870.4300 Combined Chronic Feeding and Carcinogenicity (Sprague-Dawley rat)	44024951 (1995) Acceptable/Guideline 0, 10, 100, 1000, 3000 ppm (0/0, 0.38/0.45, 3.76/4.48, 38.5/46.3, 123.4/148.3 mg/kg/day [M/F])	LOAEL = 123.4/148.3 mg/kg/day based on decreased body weight NOAEL = 38.5/46.3 mg/kg/day Increased incidence of benign liver hepatomas and/or carcinomas combined at 148.3 mg/kg/day in females

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile – Pymetrozine		
Study Type	**MRID No.**	**Results**
870.5100 Gene Mutation - *Salmonella* & E. Coli	44024952 (1991) Acceptable/Guideline 312.5 to 5000 µg/plate	Non-mutagenic (±) activation in *Salmonella* and *E.* coli.
870.5300 Gene Mutation - HGPRT with V79 cells	44024954 (1991) Acceptable/Guideline 5.21 to 333.3 µg/mL	Non-mutagenic up to the solubility limit (±) activation.
870.5375 *In vitro* cytogenetics assay in CHO cells	44024953 (1991) Acceptable/Guideline 2.58 to 330 µg/mL	Not clastogenic up to the solubility limit of the test substance.
870.5395 Micronucleus Assay in Mice	44024955 (1991) Acceptable/Guideline 0, 1000, 2000, 4000 mg/kg	No clastogenic or aneugenic response at any dose or sacrifice time.
870.5550 Unscheduled DNA Synthesis in Primary Rat Hepatocytes	44024956 (1991) Acceptable/Guideline 2.78 to 300 µg/mL	No evidence of induced UDS.
870.6200 Acute Neurotoxicity (Sprague-Dawley rats)	44411317 (1997) Acceptable/Guideline 0, 125, 500, 2000 mg/kg	LOAEL = 125 mg/kg based on decreased body temperature, FOB changes, and decreased motor activity (males) related to decreased activity NOAEL < 125 mg/kg
870.6200 Subchronic Neurotoxicity (Sprague-Dawley rats)	44411318 (1997) Acceptable/Guideline 0, 500, 1000, 3000 ppm (0/0, 35/41, 68/81, 201/224 mg/kg/day [M/F])	LOAEL = 201 mg/kg/day based on decreased weight and stereotypy (excessive head movement and sniffing) in males and tiptoe gait in females NOAEL = 68 mg/kg/day
870.6300 Developmental Neurotoxicity (Wistar-derived rat)	46170301 (2003) Acceptable/Nonguideline 0, 100, 500, 2500 ppm (0/0, 8.1/16.8, 38.7/82.6, 173.1/NA[1] mg/kg/day [gestation/lactation]) [1] NA: due to sacrifice of all animals in this group prior to scheduled termination	**Maternal:** LOAEL = 38.7 mg/kg/day based on complete litter losses NOAEL = 8.1 mg/kg/day **Offspring:** LOAEL = 8.1 mg/kg/day based on morphometric changes in the brains of female pups on PND 12 and male pups on PND 63. NOAEL < 8.1 mg/kg/day

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile – Pymetrozine		
Study Type	**MRID No.**	**Results**
870.7485 Metabolism and Pharmacokinetics (Sprague-Dawley rat)	44024957 (1993) 44517720 Classification and doses administered/regimen	Absorption and excretion studies were conducted after a single low dose iv injection (0.5 mg/kg); single low (0.5 mg/kg) and high (100 mg/kg) oral doses; 14 daily low (0.5 mg/kg) or high (100 mg/kg) oral doses followed by a single low (0.5 mg/kg) oral dose; and after a single high oral dose with the chemical labeled at different site. Both the oral and iv doses had similar urine values at 24 hours. 7 days post-dosing: recovered radioactivity in urine (56.3-80.3%), expired air (0.2-1.4%), tissues (0.3-3.8%), feces (15.4-38.9%), and cage washes (0.2-0.7%). Both sexes excreted more via the kidneys after a high dose (M/F: 72.5%/78.3%) than after a low dose (M/F: 56.3%/ 62.1%). Twelve urinary and fecal metabolites were recovered after a high dose and were isolated and characterized. There was a relatively high level of unchanged test material in the urine, which suggests metabolic saturation at the high dose of 100 mg/kg. Three major metabolic pathways: oxidation of methyl substituent at triazine ring, which is further oxidized to corresponding carboxylic acid, oxidation at methylene group within the triazine ring, and cleavage of the bridge between the two rings to give rise to several single ring metabolites. No indication that conjugated metabolites formed. Maximum blood concentrations attained at 15 minutes (0.3 ppm) and at 4 hours (60 ppm) following low and high oral dosing, respectively. Calculated half-life times ($t_{½}$) for the depletion of radiolabel from all the tissues ranged from 1 to 2 hours at 0.5 mg/kg dose (both labels) and from 2 to 11 hours at the 100 mg/kg dose, with the pyridine label having a relatively longer $t_{½}$ than the triazine label. **Details: see summaries of toxicology studies.**
870.7600 Dermal absorption (rat)	44024958 (1996) Acceptable/Guideline 0, 0.007, 0.040, 0.375 mg/cm^2 (CMC)	After 10 hours of dermal application, the percent of dose absorbed was 0.01%, 0.01%, and <0.005% for the low-, mid-, and high-dose groups, respectively. However, HED's HIARC determined that the low amount of radioactivity used may have compromised the detectability of the actual penetration and determined that an upper bound 1% dermal absorption factor would be more appropriate.

A.3. Literature Review Results

A literature search on pymetrozine using PubMed was conducted by HED on December 5, 2017.

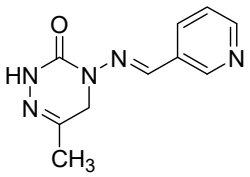
Search Terms: ((Pymetrozine)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

Results:
PubMed hits: 4
Number of Swift Articles: 1 for Animal
Number of Swift Articles: 3 for Human
Number of Swift Articles: 0 for No Tag

Table A.3. Literature Review Results for Pymetrozine

Journal	Year	Title	Reason Not Selected
Communications in agricultural and applied biological sciences	2006	Determination of pymetrozine residues in cucumber.	Not within scope (residue data)
Food additives & contaminants. Part A, Chemistry, analysis, control, exposure & risk assessment	2013	Assessment of pesticide residues in strawberries grown under various treatment regimes.	Not within scope (residue data)
Neuron	2015	TRP Channels in Insect Stretch Receptors as Insecticide Targets.	Not within scope (non-animal model)
Archives of environmental contamination and toxicology	2005	Cotton liners to mediate glove comfort for greenhouse applicators.	Not within scope (not toxicity data)

Appendix B. Physical/Chemical Properties

Table B. Physicochemical Properties of Pymetrozine	
Parameter	**Identifier**
Chemical Structure	
Physical State	Crystalline granular solid
Physical State of End-Use-Product	Water dispersible granule
Melting Point	217°C (decomposes)
Color	White to Beige
Odor	Slightly Sweet
Molecular Weight	217.23 g/mol
Density	1.36 g/mL
pH at 25°C	5.6
Vapor Pressure (25 °C)[a]	5.0×10^{-6} Pa; 3.0×10^{-8} mmHg (25°C); $< 9.7 \times 10^{-8}$ Pa (20°C)
Water Solubility	290 mg/L (25°C; pH 6.5); 270 mg/L (20°C)
Henry's Law Constant	$< 3.0 \times 10^{-6}$ Pa m^3/mol
Octanol/Water Partition Coefficient (Log K_{ow}[a])	-0.18 (25°C)

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include PHED 1.1; the AHETF database; the ORETF database; the ARTF database are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure.

Appendix D. Pymetrozine International Residue Limit Status

Table D. Summary of US and International Tolerances and Maximum Residue Limits

Residue Definition:

US	Canada	Mexico[2]	Codex
40 CFR 180.556: Plants: Pymetrozine: 1,2,4-triazin-3(2H)-one, 4,5-dihydro-6-methyl-4-[(3-pyridinylmethylene) amino]	4,5-dihydro-6-methyl-4-[(3-pyridinylmethylene)amino] -1,2,4-triazin-3(2*H*)-one		None

Commodity[1]	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[2]	Codex
Asparagus	0.04		0.04	-
Brassica, head and stem, subgroup 5A	0.5	0.5: broccoli, Brussels sprouts, cabbage, cauliflower, Chinese broccoli, Chinese mustard cabbages, kohlrabi, (napa) Chinese cabbages	0.5	-
Brassica, leafy greens, subgroup 5B	0.25	0.25: (bok choy) Chinese cabbages, broccoli raab, collards, kale, mustard greens, mustard spinach, rape leaves	0.25	-
Cotton, gin byproducts	2.0		2.0	-
Cotton, undelinted seed	0.3		0.3	-
Hop, dried cones	6.0	6: hops (dried)	6.0	-
Pecan	0.02	0.02: pecan nuts	0.02	-
Turnip, greens	0.25		0.25	-
Vegetable, fruiting, group 8	0.2	0.2: bell peppers, eggplants. ground cherries, non-bell peppers, pepinos, pepper hybrids, tomatillos, tomatoes	0.2	-
Vegetable, cucurbit, group 9	0.1	0.1: balsam apples, balsam pears, cantaloupes, chayote fruit, Chinese cucumbers, Chinese waxgourds, citron melons, cucumbers, edible gourds and muskmelons (other than those listed in this item) pumpkins, summer squash, watermelons, west Indian gherkins, winter squash	0.1	-
Vegetable, leafy, except brassica, group 4	0.6	0.6: Amaranth, arugula, cardoon, celery, celtuce, Chinese celery, corn salad, dandelion leaves, dock, edible leaved chrysanthemum, endives, fresh chervil leaves, fresh Florence fennel leaves and stalks, fresh parsley leaves, garden cress, garden pursiane, garland chrysanthemum, head lettuce, leaf lettuce, malabar spinach, New Zealand spinach, orach, radicchio, rhubarb, spinach, swiss chard, upland cress, winter purslane	0.6	-
Vegetable,tuberous and corm, subgroup 1C	0.02	0.02: arracacha, arrowroot, cassava roots, chayote roots, Chinese artichokes, chufa, edible canna, ginger roots, Jerusalem artichokes, lerens, potatoes, sweet potato roots, tanier corms, taro corms, turmeric roots, true yam tubers, yam bean roots	0.02	-
MRLs With No US Equivalent				
Lemons		0.2		
Mandarins		0.2		
Oranges		0.2		
Completed: D. Dotson: 12-4-2017				

Codex has not established MRLs for pymetrozine. Mexico has adopted the US tolerances for its export purposes.

Appendix E. Pymetrozine Occupational and Residential Exposure and Risk Estimates Summaries

A summary of the pymetrozine residential post-application exposures and non-cancer risks can be found in the Excel spreadsheet, *D444128_Appendix E Residential Post-application Gardens_Trees Non_Cancer Risks (Postapp Dermal_with DFR).*

A summary of the pymetrozine residential post-application exposures and cancer risks can be found in the Excel spreadsheet, *D444128_Appendix E Residential Post-application Gardens_Trees Cancer Risks* and *D444128_Appendix E Residential Post-application Indoor_Plants Cancer Risks (Postapp Dermal_with DFR).*

A summary of the pymetrozine spray drift exposure and risk can be found in the Excel spreadsheet, *D444128_Appendix E_ Spray Drift Risks.*

A summary of the pymetrozine occupational handler exposures and non-cancer risks can be found in the Excel spreadsheet, *D444128_Appendix E_ Occupational Handler Non-cancer Risks.*

A summary of the pymetrozine occupational handler exposures and cancer risks can be found in the Excel spreadsheet, *D444128_Appendix E_ Occupational Handler Cancer Risks (OccHndler_Cancer tab).*

A summary of the pymetrozine occupational post-application exposures and non-cancer risks can be found in the Excel spreadsheets, *D444128_Appendix E_Occupational Post-Application Non-cancer Risks Crops* and *D444128_Appendix E_Occupational Post-Application Non-cancer Risks Ornamentals* (*Occup Expo-Risk-REI Calculator* tab).

A summary of the pymetrozine occupational post-application exposures and cancer risks can be found in the Excel spreadsheets, *D444128_Appendix E_ Occupational Post-application Cancer Risks Ornamentals* and *D444128_Appendix E_ Occupational Post-application Cancer Risks Crops* (*Expo-Risk-REI Calculator* tab).

Appendix F. Summary of Registered Uses for Pymetrozine

Table F.1. Overview of Maximum Application Rates/Uses of Pymetrozine.			
Formulation [EPA Reg. No.]	**Application Equipment**	**Rep. Crop Site**	**Max App Rate**
WDG [100-912/66222-274]	Aerial, Chemigation, Groundboom	Field Crop High Acreage	0.172 lb ai/A
	Aerial, Chemigation, Groundboom,	Field Crop Typical	0.172 lb ai/A
	Mechanically-pressurized handgun		0.0172 lb ai/gallon
WDG [100-913, 100-1574, 100-1585]	Aerial	Orchard/Vineyard	0.125 lb ai/A
	Airblast, Groundboom		0.188 lb ai/A
	Mechanically-pressurized handgun		0.0025 lb ai/gallon
	Chemigation, Groundboom	Greenhouse (ornamentals)	0.313 lb ai/A
	Backpack, Manually-pressurized handwand, Mechanically-pressurized handgun		0.003 lb ai/gallon
	Aerial, Airblast, Chemigation, Groundboom	Nursery (ornamentals)	0.313 lb ai/A
	Backpack, Manually-pressurized handwand, Mechanically-pressurized handgun		0.003 lb ai/gallon
	Groundboom	Field-Grown Ornamentals	0.313 lb ai/A
	Backpack, Manually-pressurized handwand, Mechanically-pressurized handgun	Christmas Tree Farm	0.003 lb ai/gallon
	Backpack, Manually-pressurized handwand, Mechanically-pressurized handgun	Landscape (ornamentals)*	0.003 lb ai/gallon 0.3 lb ai/A
	Manually-pressurized handgun	Interiorscapes	0.003 lb ai/gallon

* Expected to result in residential exposure

Table F.2. Summary of Detailed Directions for Uses of Pymetrozine.								
Crop	**Formulation [EPA Reg. No.][1]**	**Application Equipment**	**Rep. Crop Site**	**Max App Rate**	**Max. No. App per Year**	**Min. RTI (days)[2]**	**Max. Seasonal App Rate**	**PHI (days)[3]**
Cotton	WDG [100-912/66222-274]	Aerial, Groundboom	Field Crop High Acreage	0.086 lb ai/A	2	7	0.172 lb ai/A	21
Tuberous and Corm (1C)		Aerial, Chemigation Groundboom	Field Crop High Acreage	0.172 lb ai/A	2	7	0.343 lb ai/A	14
		Aerial, Chemigation, Groundboom	Field Crop Typical	0.172 lb ai/A				
		Mechanically-pressurized handgun		0.0172 lb ai/gallon*				
Tobacco		Groundoom	Field Crop Typical	0.086 lb ai/A	2	7	0.172 lb ai/A	14
		Mechanically-pressurized handgun		0.0043 lb ai/gallon*				
Asparagus		Aerial, Groundboom		0.086 lb ai/A	NS	30	0.516 lb ai/A	170

Table F.2. Summary of Detailed Directions for Uses of Pymetrozine.								
Crop	**Formulation [EPA Reg. No.][1]**	**Application Equipment**	**Rep. Crop Site**	**Max App Rate**	**Max. No. App per Year**	**Min. RTI (days)[2]**	**Max. Seasonal App Rate**	**PHI (days)[3]**
		Mechanically-pressurized handgun	Field Crop Typical	0.0086 lb ai/gallon*				
Cole Crops		Aerial, Groundboom	Field Crop Typical	0.086 lb ai/A	2	7	0.172 lb ai/A	7
		Mechanically-pressurized handgun		0.0086 lb ai/gallon*				
Cucurbits		Aerial, Groundboom	Field Crop Typical	0.086 lb ai/A	2	7	0.172 lb ai/A	0
		Mechanically-pressurized handgun		0.0086 lb ai/gallon*				
Fruiting Vegetables		Aerial, Groundboom	Field Crop Typical	0.086 lb ai/A	2	7	0.172 lb ai/A	0
		Mechanically-pressurized handgun		0.0086 lb ai/gallon*				
Leafy Vegetables		Aerial, Groundboom	Field Crop Typical	0.086 lb ai/A	2	7	0.172 lb ai/A	7
		Mechanically-pressurized handgun		0.0086 lb ai/gallon*				
Hops		Groundboom	Orchard/ Vineyard	0.188 lb ai/A	3	14	0.563 lb ai/A	14
		Mechanically-pressurized handgun		0.0016 lb ai/gallon*				
Pecan		Aerial, Groundboom	Orchard/ Vineyard	0.125 lb ai/A	NS	7	0.25 lb ai/A	14
		Mechanically-pressurized handgun		0.0025 lb ai/gallon*				
Alfalfa (grown for seed)	WDG [WA000016, MT030008, NV000004, OR040005, ID000010, UT000010]	Aerial, Groundboom	Field Crop, High Acreage	0.086 lb ai/A	2	7	0.172 lb ai/A	14
Root Vegetables, except sugar beets (grown for seed)	WDG [OR040004]	Aerial, Groundboom	Field Crop, High Acreage	0.086 lb ai/A	2	7	0.172 lb ai/A	NS
		Aerial, Groundboom	Field Crop Typical	0.086 lb ai/A				
		Mechanically-pressurized handgun		0.0086 lb ai/gallon*				
Tomatoes	WDG [FL040006]	Aerial, Chemigation, Groundboom,	Field Crop Typical	NS	4	NS	NS	NS

Table F.2. Summary of Detailed Directions for Uses of Pymetrozine.								
Crop	**Formulation [EPA Reg. No.][1]**	**Application Equipment**	**Rep. Crop Site**	**Max App Rate**	**Max. No. App per Year**	**Min. RTI (days)[2]**	**Max. Seasonal App Rate**	**PHI (days)[3]**
		Mechanically-pressurized handgun						
Tomatoes (grown for transplant)	WDG [FL030004]	Aerial, Chemigation, Groundboom, Mechanically-pressurized handgun	Field Crop Typical	0.047 lb ai/100,000 plants 0.086 lb ai/A 0.0086 lb ai/gallon	2 prior to transplant and 2 after transplant	NS	NS	NA
Vegetable Crops (grown for seed)	WDG [WA000017]	Aerial, Groundboom Mechanically-pressurized handgun	Field Crop Typical	0.086 lb ai/A 0.0086 lb ai/gallon*	2	7	0.172 lb ai/A	14